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EXPERIMENTAL NEPHROPATHY PRODUCED BY AN ORGANO-MERCURY COMPOUND OF PHENOLSULPHONPHTHALEIN

J. EDWARD BURNS, E. C. WHITE, AND J. G. CHEETHAM

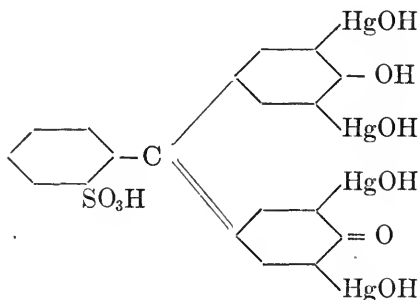
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This study was undertaken with the idea of producing acute and chronic renal lesions of varying degrees of intensity and of determining whether or not lesions could be produced more nearly resembling those found in human beings in the different types of nephritis than have been heretofore experimentally accomplished. In the production of such lesions it was thought well to use a drug which when introduced into the animal organism would by its special affinity for the cells of the renal parenchyma attack these cells directly without producing lesions elsewhere in the body of the animal. For this reason phenolsulphonphthalein, being excreted mainly by the kidney, was considered an excellent basis for the synthesis of such a drug, the theory being that anything combined with this dye might be carried directly to the kidney and there produce the desired lesions. Mercury, too, having a special affinity for the cells of the renal tubules, suggested itself as a suitable substance to be combined with phenolsulphonphthalein. It was thought that in this combination the mercury would attack these cells directly and not attack the other organs of the body, and would produce in the kidney the usual lesions of mercurial poisoning. Such a combination might be expected to produce mainly epithelial changes if given in large doses and if given in small doses over a long period of time might produce interstitial changes. As will be shown later, the existence of such lesions can be shown by chemical examination of the blood and urine, as well as by histological methods.

Unfortunately, this work has not been carried on long enough to demonstrate the extreme degree of chronic interstitial lesions which might be produced. This might require many months. From our present observations, however, we feel that enough has been shown to warrant this preliminary report and certainly enough has been found to stimulate further work along the same line.

Although a large amount of work has already been carried out upon experimental nephropathy produced by mercury, the metal has been used almost exclusively in the form of mercuric chloride. Suzuki (1) has shown that the renal lesions produced by mercuric chloride are confined mainly to the lower half of the proximal convoluted tubules; and MacNider (2) in a recent publication also considers that the renal lesions produced by mercuric chloride are most marked in that region, but he also notes some glomerular changes. He found varying degrees of susceptibility in different animals, and concluded that when death occurs before renal lesions are produced, the cause of death is shock and acidosis, the lesions produced being mainly gastro-intestinal.

The drug we have synthesized and made use of is tetra-oxy-mercury phenolsulphonphthalein. It is prepared by the action of an excess of mercuric acetate on phenolsulphonphthalein, and has the formula $C_{19}H_{10}O_5S(HgOH)_4$. It contains 63 per cent of organically bound mercury, and is probably represented structurally by the formula.



The *positions* of the mercury groups in the phthalein molecule have not been established, but those here indicated are the most

probable ones. The *number* of the entering mercury groups is definitely fixed by the analysis of the substance, which gave figures agreeing closely with the formula given above. The substance is a dark red to black powder, insoluble in water but soluble in dilute sodium hydroxide solution, giving a beautiful purple-blue solution of the sodium salt. The color is of a bluer nuance than that of the salts of phenolsulphonphthalein, and the purity of the blue is accentuated on dilution. In the experiments described in this paper the solution was prepared by dissolving a weighed amount of the material in a minimum amount of tenth normal sodium hydroxide solution and making up to suitable volume. This solution is stable for a considerable time, although on long standing a very small amount of a gray precipitate is formed. The fact that the substance is completely soluble in alkali without precipitation of mercuric oxide shows that the mercury is *organically bound*: that is, it is present in *non-ionic* form.

Using this compound, we have found varying degrees of susceptibility in different animals, as did MacNider in his experiments with mercuric chloride. In our animals, however, kidney lesions were always found, when the dose of the drug proved rapidly fatal; and some of the animals showed acute gastro-enteritis at autopsy, symptoms of its existence having been found before death. The kidneys in these animals showed a very marked destruction of the epithelium of the convoluted tubules, the cells being swollen and granular and the lumina of the tubules filled with granular and hyaline casts.

Underhill, Wells and Goldschmidt (3) also found very marked tubular lesions of a similar character in starved phlorizinized animals after the subcutaneous administration of sodium tartrate. They concluded on chemical and histological grounds, that the glomeruli were not involved. This was demonstrated chemically by the intravenous administration of a solution containing salt and urea; the salt was recovered in the urine in forty-eight hours, but there was a definite urea retention. Our animals were on the ordinary diet of 250 grams of ground meat per day and were allowed 300 cc. of water. We also gave salt and urea in-

travenously and found that in the acute type of renal injury urea was retained and the salt well excreted, while in the chronic type there was only a temporary retention of urea and no retention of salt.

After the administration of comparatively large doses of our compound (5 to 10 mgm. per kilo of body weight) there would not infrequently follow convulsive seizures with marked opisthotonos, involuntary escape of urine and feces and marked impairment of respiration, sometimes amounting to periods of apnea. The heart rate was accelerated but the cardiac contractions were strong.

In two instances the animal died in the convulsive stage, the respiration stopping long before the heart beats ceased, although prolonged artificial respiration was instituted.

Following the administration of the drug there would be diuresis for forty-eight to seventy-two hours. In the rapidly fatal cases there followed a diminished output of urine and finally there was anuria. In the acute type the urinary findings consisted of granular casts, red and white blood cells, and albumin; in the chronic type varying amounts of both hyaline and granular casts and of albumin were found.

The blood chlorides were never increased and during the stage of diuresis they were often below normal. During diuresis there would also be an increase in the output of chlorides and urea in the urine. The blood urea varied within normal limits in the chronic type, after repeating small doses, but in the acute type it increased progressively until death ensued.

The phenolsulphonphthalein output for two hours remained normal in all of our animals as long as it could be determined. Inasmuch as the drug employed in the experiments also gave rise to a purplish colored urine, it was not possible to determine the phenolsulphonphthalein output as frequently as might have been desired. When this test was made, it was definitely determined beforehand that the color in the urine due to the administration of the mercury compound had completely disappeared.

The renal excretion of the mercury-phenolsulphonphthalein compound was studied both as regards color output and output

of mercury. During its passage through the organism the substance obviously suffers cleavage into phenolsulphonphthalein and some form of mercury combination, for the urine is colored the same as if simple phenolsulphonphthalein had been administered. The feeble color of the urine on the addition of strong alkali, however, shows that only a very small amount of the dye, in whatever form it is excreted, is eliminated by the kidney.

A series of quantitative mercury determinations of the urine was made by the method of Lomholt and Christiansen (4). This method was first tried on urine to which known quantities of mercury had been added, and was found to be reliable. The following table shows the elimination of mercury for the first three days following administration of the drug in three normal dogs.

DOG	AMOUNT OF MERCURY INJECTED INTRA- VENOUSLY	AMOUNT OF MERCURY EXCRETED IN URINE		
		First twenty-four hours after in- jection	Second twenty-four hours after in- jection	Third twenty-four hours after in- jection
	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>
21	40	2.1	1.1	0.3
22	77	4.2	0.4	0.8
23	24	2.3	0.3	0.5

From this table it is seen that only very small amounts of the total mercury administered were eliminated in the urine, the largest amount being put out during the first day, the smaller amounts on the second day and third day suggesting a deposition is some part of the organism, with delayed excretion.

In considering the different types of renal lesions produced by this mercurial derivative some of the protocols of the experiments in each type will be given, as well as one of those of normal dogs to which a solution containing salt and urea was administered intravenously for the sake of comparison. Two solutions were used; one contained 9 grams of salt and 23 grams of urea to the liter (solution *x*) and the other contained double the amounts of the two substances (solution *y*). From the table of dog 19 it is seen that *before* the administration of 124 mgm. of the mercury com-

pound the intravenous injection of solution *y* caused the urea content of the blood to increase for the first three hours and to drop to normal limits at the end of twenty-four hours. The blood chlorides which were somewhat above normal after the injection dropped with the diuresis and were normal again at the end of twenty-four hours. The urea and chloride output in the urine was greatly increased for twenty-four hours. Two other normal dogs which were given the same amount of solution *y* (10 cc. per kilo) showed exactly the same reaction. However it will be seen from the table that *after* the intravenous administration of 124 mg. of mercury phthalein the blood urea increased constantly until death, except at the end of the 3 hour intervals, when it was slightly decreased. This increase had begun before the injection of solution *y*, but it was not so great comparatively during the three hours following the injection as it was during the preceding twenty-four hours, or during the following eighteen hours. The blood chlorides which were subnormal before the experiment was begun, showed a slight increase at the end of six hours and were greatly diminished during the experiment, and the bladder was empty at autopsy. The urea and chlorides in the urine were greatly diminished during the experiment, the urea output being practically nothing. The dog had continuous nausea and vomiting for eighteen hours preceding death and there were slight convulsive jerkings of body and legs. There was some flow of saliva from the mouth and a blood tinged vaginal discharge, but no evidence of gastro-enteritis. Dog 19 may be considered typical of the acute type (table 1). There were four other animals of this type and all died in from five to fourteen days. The doses of the mercury compound given were from 4 to 10 mgm. per kilo of body weight. There was hemorrhagic gastro-enteritis in two of these animals and they all suffered loss of weight. The urine showed increasing amounts of albumin and casts and red and white blood cells.

The chronic type of renal lesion produced by small repeated doses of the mercury phthalein was found in dogs 13, 14 and 17. These animals did not lose weight. They had occasional convulsive seizures after administration of the drug, and once or

twice there was slight nausea and vomiting and slight diarrhea following the injection. The urine showed varying amounts of albumin and casts. The general health of the animals remained good. The total amounts of the drug received by these dogs varied from 312 to 372 mgm. and the doses received at a single time varied from 1.5 to 10 mgm. per kilo of body weight. The duration of the experiments was from fifty-two to sixty-five days.

TABLE 1

Dog 19

DATE	WEIGHT	Hg PHENOLBULPHON-PHTHALEIN GIVEN INTRAVENOUSLY	SOLUTION \times GIVEN IN-TRAVENOUSLY	BLOOD		URINE					
				Urea per litre	NaCl per litre	Total output	Urea in total output	NaCl in total output	Albumen	Casts	Hours collections of urine
	kgm.	mgm.	cc.	grams	grams	cc.	grams	grams			
May 17.....	13.0			0.162	5.375	80.0	3.34	0.284	0	0	24
May 22, A, 10.30 a.m.....			130	0.366	6.61	152.0	6.694	0.6232			3
May 22, B, 1.30 p.m.....				0.51	6.0	255.0	4.023	0.918			3
May 22, C, 4.30 p.m.....				0.336	6.125	95.0	1.995	0.513			3
May 23, 10.30 a.m.....				0.246	5.375	170.0	8.0272	1.7			24
May 24.....		124									
May 25.....				0.612	5.437						
May 27.....				3.0					++	+	
May 28, A, 9.30 a.m.....	11.1		110	4.002	4.275	123.0	0.15867	1.0578			3
May 28, B, 12.30 p.m.....				4.374	4.187	11.0		0.0506			3
May 28, C, 3.30 p.m.....				4.028	4.615	10.5	0.0063				3
May 29, 9.30 p.m....		Dog died		5.88	4.125						

The administration of the drugs was usually followed by diuresis lasting from forty-eight to seventy-two hours. There was only a slight and temporary increase in the blood urea and the blood chlorides were normal or slightly below normal during the diuresis. The urine urea decreased as a whole except in the case of dog 13, in which there was an increased output towards the end of the experiment. The chloride output in the urine varied, being

increased on the whole in dogs 13 and 14 and decreased in dog 17. The phenolsulphonphthalein output for two hours remained normal in all of these animals. After intravenous injections of solutions *x* and *y* there was a transient increase in blood urea and the blood chlorides remained normal or became subnormal during diuresis. The urine urea showed a transient increase except after the administration of solution *y* in dogs 14 and 17 where there was diminished output. The urine chlorides showed an increased output except after the administration of solution *y* in dog 17 (tables 2, 3 and 4).

HISTOLOGICAL DESCRIPTION

Acute renal lesions. These are mainly of the epithelial cells of the convoluted tubules. These cells show swollen and granular protoplasm, the nuclei in places being rather pale and showing disintegration. The swelling of the cells is so great as to occlude completely the lumina of the tubules of places. In other regions, particularly towards the region of the capsule, the cells have become entirely disintegrated, and the tubules contain granular and hyaline casts (fig. 1). The cells lining the connecting tubules seem normal. Their protoplasm is rather deeply stained and the same thing is true of the cells of the loop of Henle and of the connecting tubules. There is no increase in interstitial tissue. The glomeruli are everywhere intensely congested, the capillaries being greatly engorged with blood cells. The glomeruli are swollen, in some instances completely filling the capsular space. The nuclei of the endothelial cells are darkly stained. In some places the tufts of capillaries of the glomeruli have become agglutinated. It is impossible, however, to make out any adhesions between them and the outer layer of the capsule of Bowman. The blood vessels throughout the kidney show a well marked congestion without any evidence of hemorrhage. There is no round cell or polymorphonuclear infiltration.

Chronic renal lesions. In this type the lesions are also mainly in the convoluted tubules but there are also glomerular changes. With the lower power of the microscope there are seen areas in

TABLE 2

Dog 13

DATE	WEIGHT	Hg PHENOL- PHTHALEIN GIVEN INTRAVENOUSLY	SOLUTION GIVEN IN- TRAVENOUSLY	BLOOD		URINE					
				Urea per litre	NaCl per litre	Total output	Urea total out- put	NaCl in total output	Per cent Phthalein in 2 hours	Albumen	Casts
March 25...	8.3	mgm.	cc.	grams	grams		grams			0	0
March 25...		10.0		0.264	0.125	50	0.6	0.425	65	0	0
March 27...				0.276	6.25	218	2.66	0.8848	82	Trace	Few
April 2.....				0.204	5.25						
April 3, A, 10 a.m....			150	0.272	6.875	170		0.34		Trace	Few
April 3, B, 1.30 p.m....				0.468	5.75	52	1.946	0.208		Trace	Few
April 3, C, 4.30 p.m....				0.3	5.75	122	3.967	0.6588		Trace	Few
April 4, 11 a.m.....				0.336	6.25	105	2.066				
April 9.....	8.0	24.9									
April 11.....				0.216	6.0						
April 12.....						24	0.94	0.07		+	+
April 15.....	8.2	24.6		0.384					77		
April 17.....											
April 18.....						130	4.381	0.221		+	+
April 19, A, 10.30 a.m.				0.338	6.375	32	1.52	0.0512			
April 19, B, 1.30 a.m....			150	0.36	5.5	110	2.943	0.704			
April 19, C, 4.30 a.m....				0.408	6.125	35	1.003	0.112			
April 20 10.30 a.m.				0.192	6.375	148	4.476	0.3552			
April 22.....	7.3	21.9		0.24	5.875					++	Few
April 24.....											
April 25.....	7.5	37.5		0.48	6.25					Faint trace	+
April 26.....						220	5.029	0.76		Trace	
April 27.....									10(?)		
April 30.....	8.2	41.0				245	5.713	0.539			
May 2.....				0.39	5.75					Trace	Few
May 6.....	8.2	41.0								+	Few
May 6.....									65		
May 8.....				0.492	5.25						
May 9.....											
May 10.....	7.9	59.0		0.384	5.375					Faint trace	+
May 13.....					5.125						
May 14.....											
May 15.....				0.3		418	5.2668	1.9228			
May 16.....	7.3	90.0	Dog died immediately after injection, convulsion. Respiration stopped before heart							+	+

TABLE 3
Dog 14

DATE	WEIGHT kgm.	H _g PHTHALEIN GIVEN mgm.	N SOLUTION GIVEN cc.	BLOOD		URINE						
				Urea per litre grams	NaCl per litre grams	Total output cc.	Urea in total output grams	NaCl in total output grams	Per cent phtthal- in 2 hours	Albumen	Cast	
March 25.....	6.6			0.192	6.56	96	2.119	0.6432	70	0	0	
March 27.....		10.0		0.24	Lost	118	1.73	0.236	80	+	0	R.B.C. (trauma)
April 2.....				0.18	6.25							
April 3, A, 10.30 a.m.			150	0.246	6.375	202		0.242		Trace	Few	1.028 alk.
April 3, B, 1.30 p.m.				0.408	5.875	64	2.296	0.2432		Trace	0	1.020 alk.
April 3, C, 4.30 p.m.				0.25	6.0	65	2.09	0.364		Faint trace	Few	1.028 alk.
April 4, 11 a.m.....				0.156	6.25	105	1.19	0.819				
April 9.....	6.6	19.8										
April 11.....				0.18	5.56	105	0.21	1.7	75	++	+	
April 12.....												
April 15.....	6.8	20.4										
April 17.....				0.336	6.0	140	3.948	0.14		++	+	
April 18.....						112	3.48	0.0				
April 19, A, 10.30 a.m.			150	0.222	6.625	58	2.16	0.2668				
April 19, B, 1.30 p.m.				0.318	6.75	32	1.317	0.1216				
April 19, C, 4.30 p.m.				0.384	6.25	100	2.748	0.4				
April 20, 10.30 a.m.....				0.204	6.625							

EXPERIMENTAL NEPHROPATHY

[illegible]

TABLE 4

Dog 17

DATE	WEIGHT	Hg. PHENOLSULPHON- FTHALAIN GIVEN INTRAVENOUSLY	SOLUTION $\frac{1}{2}$ GIVEN INTRAVENOUSLY	BLOOD		URINE					
				Urea per litre	NaCl per litre	Total output 24 hours	Urea in total output	NaCl in total output	Per cent phthalain 2 hours	Albumen	Casts
	kgm.	mgm.	cc.	grams	grams	cc.	grams	grams			
April 6.....	7.6			0.168	6.0	120	2.709	0.516	61	0	0
April 9.....		22.8									
April 11.....				0.27	4.87(?)						
April 12.....						122	2.23	0.12		+	+
April 15.....	7.6	22.8							75		
April 17.....				0.36	6.25						
April 18.....						35	0.7896	0.0225		Faint trace	Few
April 19, A, 10.30 a.m.....			150	0.252	6.625	86	3.908	0.1806			
April 19, B, 1.30 p.m.....				0.288	6.25	50	1.654	0.53			
April 19, C, 4.30 p.m.....				0.384	6.625	32	1.44	0.1088			
April 20, 10.30 a.m.....				0.216	6.375	110	3.47	0.286			
April 22.....	7.3	36.0								+	0
April 24.....				0.42	5.625						
April 25.....	7.3	36.5									
April 26.....				0.60	5.375					Trace	+
April 27.....						170	3.838	0.102		Trace	
April 30.....	7.3	36.5							65		
May 2.....				0.42	5.81	45	1.313	0.225			
May 6.....	7.5	37.5		0.704	5.875					++	++
May 8.....										++	Few
May 9.....				0.486	5.5				60		
May 10.....	7.05	52.5				122	1.34	0.1952			
May 13.....				0.54	5.937(?)					++	+
May 14.....				0.516	4.875						
May 15.....				0.258	4.65	26	0.2527	0.208			
May 16.....	6.8	68.0								++	0
May 17.....				0.312	3.75					+	+
May 22, A, 10.30 a.m.....	6.6		66	0.672	5.937	105	1.694	0.0315			
May 22, B, 1.30 p.m.....				0.324	5.875	9					
May 22, C, 4.30 p.m.....				0.552	5.375	33	1.1276	0.0066			
May 23, 10.30 p.m.....				0.504	6.125	7					
May 27.....	7.7									++	+
May 29.....			Do g sac rificed.								

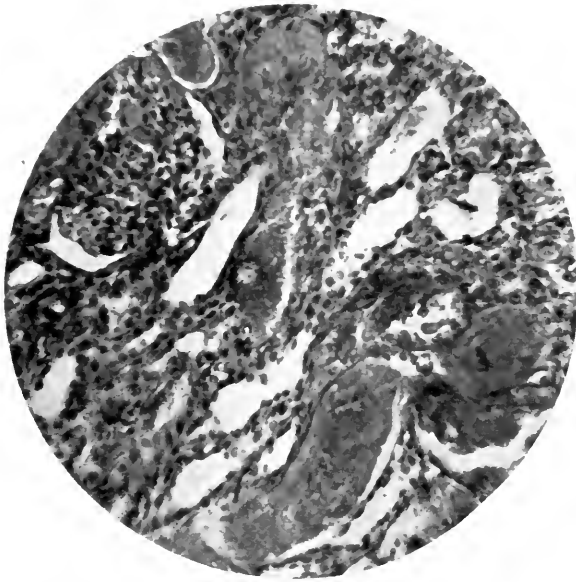


FIG. 1. PHOTOMICROGRAPH SHOWING GRANULAR AND HYALINE CASTS IN THE LUMINA OF THE CONVOLUTED TUBULES AND SWELLING OF THEIR TUBULAR EPITHELIUM WITH DISINTEGRATION OF ITS NUCLEI

There is also seen one congested glomerulus with dark-stained nuclei of its endothelial cells.

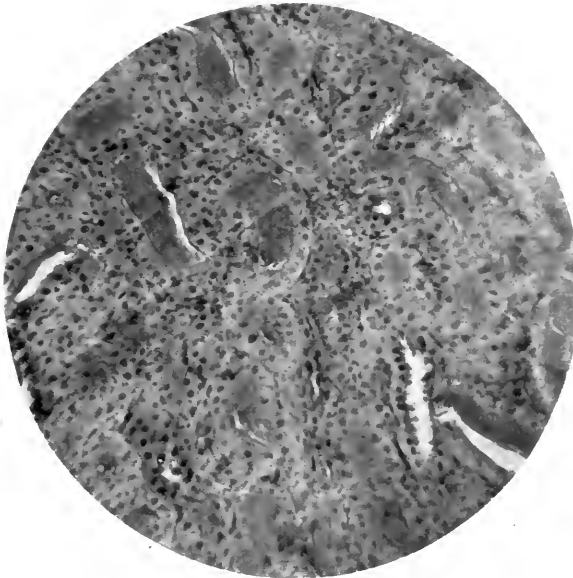


FIG. 2. PHOTOMICROGRAPH SHOWING SWELLING OF CELLS OF CONVOLUTED TUBULES WITH PALING AND IN PLACES COMPLETE DISAPPEARANCE OF THEIR NUCLEI

The lumina of these tubules are filled with a pink staining granular material.

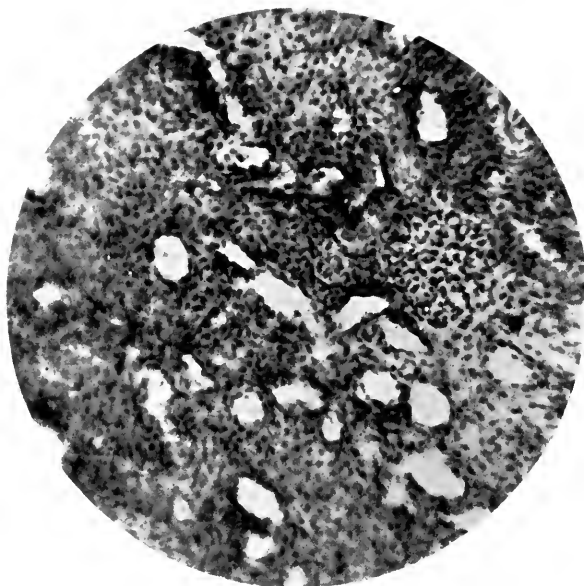


FIG. 3. PHOTOMICROGRAPH SHOWING GREAT INCREASE IN INTERSTITIAL TISSUE
AND THE DISAPPEARANCE IN PLACES OF THE EPITHELIAL LINING OF
THE TUBULES



FIG. 4. PHOTOMICROGRAPH SHOWING COMPLETE FIBROSIS OF THE GLOMERULI
Their outlines can be indistinctly made out.

which it would seem that the convoluted tubules had for the most part been completely obliterated, only a few scattered ones being patent. This change is accompanied in places by an increase in interstitial tissue. The glomeruli are scarcely visible in these areas being seemingly almost homogeneous with the surrounding tissues. With high power, outlines of the convoluted tubules can be made out in these areas but the cells are greatly swollen and the nuclei have become very pale and in places have disappeared almost completely. The cells have become so swollen that they fill the lumina completely, other areas being occupied by a darker pink staining material (fig. 2). In other places the tubules have been entirely stripped of their lining epithelium or the portion of the cells containing the nucleus and lying next to the basement membrane alone remains. There are also areas in which the interstitial tissue has been very markedly increased (fig. 3). The glomeruli completely fill Bowman's capsule for the most part and definite inroads of fibrous tissue, amounting to complete fibrosis in places, can be made out (fig. 4). There is no engorgement of the capillaries of the glomeruli or other blood vessels throughout the kidney. There is no round cell or polymorphonuclear infiltration.

SUMMARY

1. The renal lesions produced by the administration of tetra-oxymercury phenolsulphonphthalein resemble quite closely those found in the different types of nephritis in human beings and it is hoped that by a further study lesions of the very extreme chronic type can be produced, such as the small contracted kidney with its accompanying cardio-vascular changes.

2. The lesions of the acute type are mainly tubular, although some slight glomerular changes have been noted.

3. In the chronic type the most striking change is the increase of interstitial tissue both in the glomeruli and between the tubules, together with areas of tubular obliteration and of glomerular fibrosis.

4. Chemical examination of the blood and urine has shown results quite analogous to the type of lesions produced.

5. This organo-mercury compound has, as was anticipated, produced these marked renal lesions without producing lesions elsewhere in the body in the chronic type and in the acute type the lesions other than renal have been insignificant and in no case responsible for the death of the animal.

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“FORAGE DE LA PROSTATE” IN THE TREATMENT OF PROSTATIC HYPERTROPHY

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The treatment of prostatic hypertrophy by “Forage de la Prostate” has as its object the gouging out of a tunnel from the interior of the gland through the natural channels, in such a way as to permit the free escape of urine. Study of the anatomic relations of the prostate shows that this operation is indicated in many cases. Examination of the gland by rectal touch does not disclose the actual shape of the obstacle to urination. The distortion of the prostatic urethra can only be learned by means of careful urethroscopic examination. “Forage de la Prostate” is a surgical intervention carried out under direct ocular observation.

Certain conditions have been found invariably present in the very numerous urethroscopic observations which we have carried out during the last fifteen years or more. First of all the hypertrophy is always characterized by an elongation of the “prostatic fossa,” viz., that part of the prostatic urethra comprised between two fixed points, the neck of the bladder behind and the posterior border of the verumontanum in front. This elongation may be considerable and may reach an antero-posterior length of 6, 8, or even 10 cm. Furthermore the true causes of the mechanical interference to urination due to prostatic hypertrophy appear to be chiefly two. The first is the elevation of the bladder neck known as the prostatic bar; a true dam separating bladder and urethra, preventing the emptying of the bas-fond of the bladder, in the form of a gable roof, falling away toward the bladder at an obtuse angle, and toward the urethra at a steep angle, almost vertically. The second, almost as important as the first, is the squeezing together of the hypertrophied lobes, forming a very irregular antero-posterior tunnel.

The history of the treatment of prostatic hypertrophy has been so fully described in Proust's book, "*La Prostatectomie dans l'Hypertrophie de la Prostate*," 1904, that we need not go into it fully. We may simply recall Bottini's operation which certainly gave some good results but did not long retain its popularity, for after this intervention, made completely in the dark, incontinence of urine might ensue, while the mortality of the operation was by no means negligible. The operation devised by Prof. Hugh Hampton Young (of Baltimore) and entitled by its originator, the "punch operation," is far more important and interesting. Prof.



FIG. 1. THE USUAL APPEARANCE OF BLADDER NECK AND PROSTATIC BAR BEFORE TREATMENT

Hugh Hampton Young was, indeed, the first to attack the prostate by the endourethral route.¹ For this purpose he employs a urethroscopic tube 18 cm. long, the vesical extremity of which is slightly curved to facilitate its introduction into the posterior urethra, below which beak there is a fenestrum which can be drawn over the prostatic bar under direct observation in such a way as to cover it quite completely. This urethroscopic tube is illuminated externally. The "punching" is performed by a second tube slipping into the outer one, acting as a guillotine under ocular control, cutting away the prostatic bar and thus removing the obsta-

¹ American Medical Association meeting, Atlantic City, June, 1912.

cle to urination. This ingenious procedure is extremely interesting and with it Professor Young has obtained excellent results under various conditions. The only criticism we venture to make of it is that, although the operation does indeed guillotine the bladder neck, it attacks only this and its action can not be graduated. Moreover it can have but slight effect upon the lateral lobes.

We may also note in passing the operation of prostatectomy. This was originally performed by the perineal route, the technique of which was perfected by Albarrin, Proust and Gosset. The

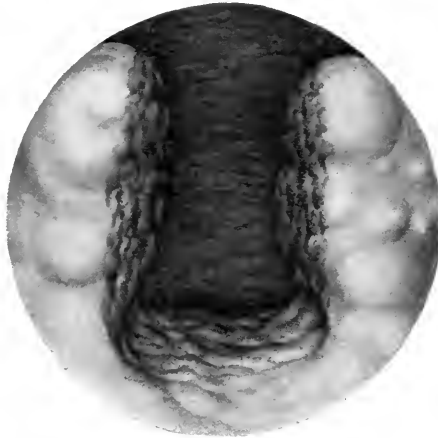


FIG. 2. PROSTATIC BAR PARTIALLY GOUGED OUT

many reports of Freyer have shown that the prostate may be readily removed by the hypogastric route. According to this technique the prostate is enucleated through the bladder. This is transvesical prostatectomy, made familiar to the French by the work of Pauchet. Transvesical prostatectomy is an excellent operation when the prostate is very large and the retention considerable but its use should be restricted to such cases. In most cases the operation is out of all proportion to the symptoms observed. It is not the operation of choice for small hypertrophies or incomplete retention. Moreover in spite of the perfection of technique during the last few years, prostatectomy is still, even

in the hands of the most accomplished operators, beset with dangers. These dangers are to be foreseen chiefly in patients with infection of the posterior urethra and bladder. For such cases prostatectomy is formally contraindicated.

Thus to fill the gap another operative procedure is required. "Forage of the prostate" fills the need for it is without danger and may even be performed upon patients with such grave renal insufficiency as to prohibit any grave surgical intervention. Its results are not only equal to but superior to those obtained by prostatectomy, as witness the following case:

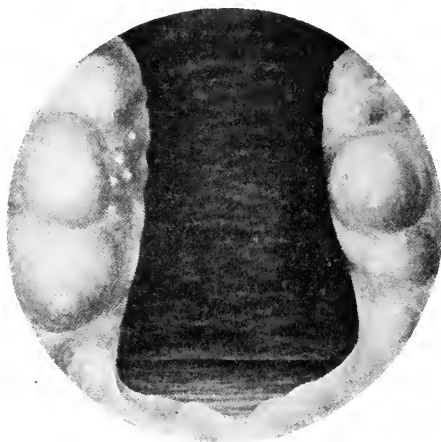


FIG. 3. PROSTATIC BAR COMPLETELY DESTROYED; BLADDER BASE LEVEL WITH THE FLOOR OF THE BLADDER NECK

A man, sixty years of age, consulted four distinguished surgeons who were unanimous in diagnosing his ailment as due to his prostate and in recommending prostatectomy by the suprapubic route. He submitted to this operation and at the end of three months his wound was healed. But, inasmuch as the four surgeons consulted before the operation had assured him that his urination would be easy and painless thereafter, he was painfully surprised to find that not only was urination more difficult than before operation, but that his urine now contained pus and blood. In this distressful condition he consulted my friend, Dr. Pauchet, who referred him to me. The cause of his difficulty was readily ascertained. The remains of his prostate obstructed the urethral canal

and were the cause of some of his symptoms. Moreover some prostatic fragments had fallen into the bladder and become incrustated with urinary salts, thus forming calculi, which I undertook to remove by litholapaxy. On withdrawing the lithotrite I found in the grasp of the instrument a fragment of prostate about 3 cm. long which had fallen into the bladder during the prostatectomy, become gradually incrustated with calcareous salts and thus originated his calculi. I subsequently destroyed the fragments of prostate obstructing the urethra by galvano-cauterization and electro-coagulation, thus rapidly relieving his symptoms. The blood disappeared from his urine which became clear and his micturition normal.

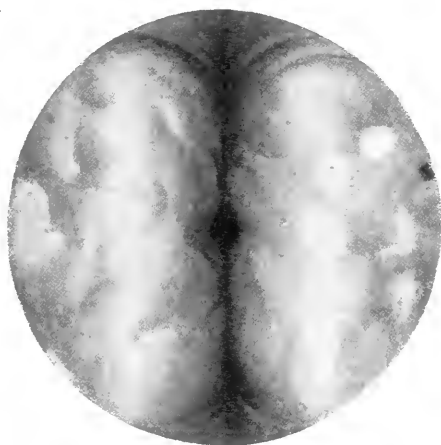


FIG. 4. ASPECT OF THE LATERAL LOBES OF THE PROSTATE, THE CLOSE APPPOSITION OF WHICH INTERFERES WITH MICTURITION

“Forage of the prostate,” the operation which I have developed, and reported upon first in 1914² is not an operation properly so called. The patient requires no confinement in hospital. He may return home immediately after the procedure. The prostatic obstacle to urination is simply suppressed without danger to the patient.

The procedure may be described in imaginative language as follows: When a mountain interferes with communication between two points, this communication is established, not by removing the whole mountain, but by digging through it a tunnel

² Paris Chirurgical, May, 1914, No. 5, p. 516.

sufficient to care for the traffic. This is what we do to the prostate. Why remove the whole gland when urination may be made normal by digging a tunnel through it? This tunneling of the prostate is performed through my direct vision cystoscope, which I have sufficiently described elsewhere.³ Through this instrument two different procedures may be performed: the one attacks the elevation of the bladder neck and destroys the prostatic bar; the other opens a passage through the prostatic tunnel between the prostatic lobes. The hypertrophied portion of the prostate is destroyed by the galvano cautery, "a knife of fire"



FIG. 5. THE FORAGE OF THE LATERAL LOBES OF THE PROSTATE IS BEGUN AT THE CENTER

which acts with the greatest rapidity. It cuts out the prostatic lobes just as a knife cuts a potato. Its action is rapid but excites some bleeding. If this is marked the galvanic knife can not control it. One must employ electro-coagulation, as was first suggested by Doyen. This checks the hemorrhage with astonishing rapidity. The coagulation acts like an artery clamp on a bleeding vessel. The small scab resulting from electro-coagulation is very adherent and gives rise to no subsequent bleeding.

One must employ galvano-cautery knives of various types. Although a thin knife may suffice to incise the urethral mucosa,

³Traite d'Ureteroscopie et de Cystoscopie, Luys, 1914.

the denser tissue of the prostatic adenoma can only be cut by a very stiff and strong blade. In fact the tissue of the prostatic adenoma is often very difficult to cut. It has the consistence of a full rubber ball over which the incandescent cautery may slip without cutting. Heavy blades are required to cut into it and destroy it. The cautery knives should have various shapes. A knife blade suffices for the prostatic bar but curved blades set at a right angle are required to scoop out the lateral lobes like a potato, and circular blades are required to ream out the circumference of the prostatic canal.

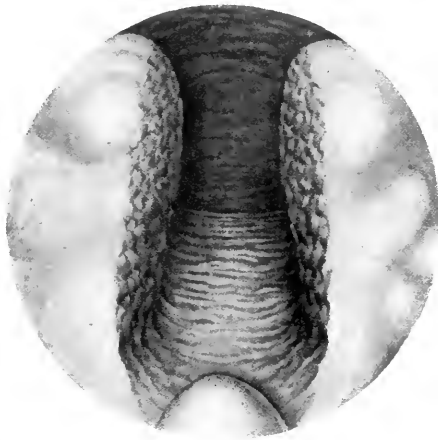


FIG. 6. THE DESTRUCTION OF THE PROSTATIC LOBES EXTENDS THROUGHOUT THEIR WHOLE DEPTH AND LENGTH. THE URETHRAL LUMEN IS WIDE OPEN FROM VERUMONTANUM TO BLADDER

We repeat, "forage de la prostate" has given us absolutely satisfactory results. These good results are durable as well as immediate. One of my first patients, operated upon more than four years ago, recently returned for reëxamination. I found his condition perfect; his retention had never returned. Two capital results are claimed for this operation: the complete disappearance of the preëxisting residuum and the return of force to the urinary stream. Some thirty cases observed up to the present writing have given uniformly perfect results. This

method of treatment we therefore look upon as most promising, a new lead which will certainly be followed because it will prove most acceptable to the patient who will not have to look forward to at least six weeks in hospital and who will avoid the risks of a major surgical operation.

ABSTRACTS OF THE TRANSACTIONS OF THE UROLOGICAL CONGRESS, PARIS, OCTOBER 7-8, 1918

A). THE TREATMENT OF GONORRHEA IN THE ARMIES AND IN THE INTERIOR

Dr. J. Janet: The increase in the number of venereal cases as a result of the war is incontestable but it is not as striking as one would first believe considering the number of men mobilized. In the early days of the war the infections were more frequent in the military zone than in the interior. The reverse however is true since the institution of sanitary measures in the military zone and in the barracks. The treatment of gonorrhea among combatants should consist only in the use of balsams, irrigations being used only during periods of rest. In the hospital of the barracks and in the interior the treatment of gonorrhea does not differ from the therapy usually employed. The abortion treatment of gonorrhea, which is the ideal one is successful in about two-thirds of the cases, providing it is begun within twelve hours after the appearance of the discharge. It may be attempted later but with less chance of success. It consists in giving for a period of three days urethral injections of 20 per cent argyrol, preceded by anterior urethral irrigations of argyrol in the strength of 1 : 500. During this period the patient himself should also carry out urethral injections with 10 per cent argyrol after each voiding. The argyrol should be retained within the urethra for five minutes. The treatment which has given the best results consists of irrigations of potassium permanganate, anterior in cases of anterior urethritis, anterior and posterior in the event of involvement of the entire urethra. Gradually increasing strengths of solution, ranging from 1 : 10,000 to 1 : 4,000 and inversely proportional to the acuteness of the inflammation, are employed. Two irrigations a day are necessary in cases of acute gonorrhea. Irrigations should be commenced immediately, however acute the condition may be. In cases of very acute inflammation of the entire urethra, it is well for a day or two to confine the irrigations to the anterior urethra. Irrigations should never be suspended in case of the development of a complication, for instead of being harmful, they exercise a very favorable influence on its course.

The cases of prostatitis whose chief symptom is persistent urinary difficulty which fail to respond to irrigations of average strength should

be treated with very weak solutions, say 1 : 20,00 to 10,000, without any massage. This latter treatment should be given only to cases of gonorrheal prostatitis which are free from all acute manifestations.

The cases of epididymitis likewise treated with very weak irrigations clear up rapidly enough without resorting to the useless procedure of puncture of the epididymis or of intra-epididymal injections of electrargol.

Gonorrheal arthritis which is usually treated by irrigations seems to be favorably influenced by the employment of gonorrheal vaccine. In view of the fact, it would seem wise to combine the two treatments.

Gonorrheal prophylaxis by very early injection of antiseptics is certainly very promising, as has been established by the results obtained in the American Army. There is still need however of standardizing this treatment in regard to technique and strength of solution used.

Dr. Cathelin emphasizes the importance of gonorrheal infection from a military standpoint. He considers the advisability of sharply dividing the Urological from the Dermato-Venereal Centers in the treatment of cases of urethritis and insists on the necessity of a greater uniformity of treatment of gonorrhea in the different centers with reference to the employment of permanganate. He is of the opinion that the treatment of chronic posterior urethritis should be postponed until after the war, at which time it can be treated more satisfactorily. He is also of the opinion that the use of vaccines is very successful in the complications of gonorrhea but has no effect upon the course of urethritis itself. He gives the statistics of the Urological Centers of the 5th district which had treated in hospital almost 300 cases of uncomplicated urethritis and 704 complicated cases. The remaining cases numbering almost 25,000 were treated in the dispensary. He approves, with some reserve, of the American method of prophylaxis.

Dr. Georges Luys favors the treatment of gonorrhea epididymitis by intra-epididymal injections of electrargol combined with hyperemia. In most then 100 closely observed cases, he has always been able to find a decrease in the inflammatory phenomena following this treatment. In most cases the patient is able to get up after four days and it is at this time that hyperemia should be used in order to hasten the disappearance of the indurated nodules. This is obtained by compression of the spermatic cord.

Dr. Paul Hamonic protests against the epithet "barbarous" as applied to his treatment of epididymitis by interstitial injections of colloidal silver. If his method had merited the adverse criticism of Dr. Janet, he would not have treated the hundreds of cases and would not have obtained the complete acceptance of his ideas by Drs. Asch of Strasburg, Doré Desvignes of Paris, Braendle of Breslau, Vignolo Lutati of Turin, Gennerich and Rohrbach of Kiel, Mario Giordano and Adolfo Tomiselli who have published numerous observations. In chronic cases, colloidal silver may be injected in large doses without producing much pain but in acute gonorrheal epididymitis, it is necessary to proceed very cautiously as the tissues are extremely sensitive. It is not the contact of the silver with the tissues but their distension which produces the pain. It is necessary therefore to inject slowly the smallest volume of a colloidal preparation as rich as possible in silver. The solutions prepared by the electrical method are much less painful than the ones obtained chemically. Properly applied the method is only slightly painful and in every case the suffering is transitory. The reaction is insignificant and the cure rapid. If the sterilizing injection is employed at the very outset of the epididymal infection, no secondary induration is produced but if, at the time it is practised a nodule has already formed in the epididymis, the latter persists for some time.

Dr. P. Hamonic reviews the treatment of rebellious cases of chronic gonorrhea by the insufflation of iodine vapors which he published in 1888 and in 1912. He urges the necessity of employing the vapors of iodine instead of the tincture or the aqueous solution, the former being too irritating, the latter too inefficient. These vapors, very well tolerated by the urethral and vesical mucosa, produce a most energetic disinfecting action when used in chronic urethritis. In the bladder Dr. Hamonic insufflates by means of a hollow sound and in the urethra he employs a hollow sound containing a central tube. Between the latter and the sound is a free space for the return of the insufflated vapor. The vapors are produced by moderately warming a glass ampule containing metallic iodide and a bellows is used to force the vapor in. The action is very powerful against the organisms contained within the epithelial cells and the tolerance of the tissue is uniform. A slight inflammatory reaction of short duration follows each insufflation and the purulent discharge is rapidly changed into a serous one which disappears in turn.

Dr. Pasteau insists upon the organization of the genito-urinary service in the armies. He shows how the centers of diagnosis and treatment are able to operate, whether the army be in camp or in the field. The treatment of gonorrhea, either simple or complicated becomes easy and the results obtained satisfactory. As regards venereal prophylaxis, it is wise to avoid giving the impression that the methods, whatever they may be, insure against all possibility of infection, either in case of syphilis or gonorrhea. It is far preferable to state clearly that he who exposes himself to infection is always running the risk of acquiring it and to persuade patients that it is to their interest to obtain treatment as soon as possible after the appearance of symptoms. The increase in the number and the permanence of treatment centers and their better organization are necessary in order to secure results superior to those obtained today.

Dr. E. L. Keyes of New York insists upon the methods of prophylaxis against gonorrhea employed in the American Army and declares that in a series of 60,000 cases only 1 to 2 per cent of failures are recorded.

Dr. Le Fur in the treatment of acute gonorrhea employs the methods of irrigation with permanganate in solutions of 1 : 6,000 and 1 : 4,000, even decreasing the strength in very acute cases to 1 : 8,000. Injections of 10 and 20 per cent argyrol are also used. This method of irrigation should not be continued for too long a period and as soon as the case has become subacute, that is to say, after about a month of urethro-vesical irrigations, dilatation should also be carried out. The dilatations should be given carefully and progressively, and instead of having an unfavorable effect upon the course of subacute and chronic gonorrhea, they unquestionably hasten the cure. Instillations of protargol and silver nitrate should not be employed in urethritis while the gonococcus is present for they provoke recurrences. In cases of gonorrheal cystitis, however, vesical instillations have a very beneficial effect. The abortive treatment of gonorrheal urethritis should be carried out almost exclusively with injections of 10 to 20 per cent and irrigations of 5 and 10 per cent argyrol.

In the cases of epididymitis the author has obtained good results from epididymal injections of electrargol which lead to a rapid disappearance of pain and swelling.

In cases of prostatitis massage of the prostate or in more exact terms "glandular expression of the prostate" is especially indicated and should be carried out alternately with high dilatations. Irrigations of the posterior urethra with a mechanical dilator may be advised at this point.

The cases of seminal vesiculitis which are more frequent than is usually supposed are in general very resistant to treatment and they explain those cases of recurrent infections where the disease was apparently cured.

The use of the gonococcal vaccine of Nicolle is followed apparently by more satisfactory results in the complications of gonorrhea, than in the disease itself.

Dr. Escat of Marseille reports 2254 cases of gonorrhea, 1208 of which were treated in the infirmary of the garrison, 629 at the Dermato-Venereal Center and 354 at the Urological Center. The majority of the last mentioned were cases of complicated gonorrhea. From the standpoint of the service, the individual and the community, the treatment of gonorrhea in the interior is far from what it should be. The author concludes: (1) That the treatment of simple gonorrhea or the more rebellious types without appreciable cause deserves to be better organized in the regimental infirmaries. The French method of irrigation advised by Janet could be easily and systematically carried out in the infirmary either in the form of an abortive treatment or as a routine method. The vaccines have given as yet either deceiving or doubtful results. (2) Cases of complicated gonorrhea should be treated only in the Urological Centers.

The complications are either acute or chronic. For the cases of acute adenitis, irrigation is the method of choice after the subsidence of the inflammation or after incision of the glands. For the cases of prostatitis he emphasizes the uselessness and danger of too early massage, particularly when this procedure fails to express secretion. In cases of severe epididymitis, epididymotomy such as he advised in 1903 is the treatment of choice for it allows the patient to get up and resume irrigations. In cases of chronic complications without stricture he insists upon their immediate return to the army. All cases of urinary fistula, however, whether of follicular or Cowperian origin should be operated upon and allowed to recuperate. In cases of gonorrhea complicated by such lesions as phimosis, vegetations, chancroid, chancre, etc., it is more often of advantage to employ surgical intervention. In urethral stricture he always employs irrigations and careful urethral dilatations.

Dr. Lebreton thinks that the best method of attacking the gonorrhea problem in the army and the one which would facilitate rapid recuperation of all the cases which fill the regimental infirmaries or the special

hospitals might be found by the creation of so called "Abortion Centers" especially in the cities possessing a Urological or Venereal Center. To these points, the soldiers, duly warned and under threat of punishment, in case of delayed declaration, would be directed as soon as possible after the appearance of symptoms and being watched and treated in a scientific fashion would be cured rapidly.

Dr. Barbellion believes that in the detection of latent gonorrhea, microscopic examination or even cultures of the urethral secretion are insufficient. Ejaculations permits one to obtain the entire secretion of the genital glands and cultures from the products of ejaculation often show gonococci after failure to demonstrate the organisms by other methods.

Dr. Minet insists upon the dangers of dilatation during the course of gonorrhea. With the majority of urologists he opposes the inexact and dangerous assertion that the treatment of gonorrhea is ended only when dilatation has been performed. Gonorrhea tends to a spontaneous cure, especially if all traumatism to the canal is avoided. Dilatation is to be recommended only in cases where chronic foci of infection are present in which case it should be localized at these points.

Dr. Pousson: The ideas presented by our colleague Le Fur on the necessity of completing treatment in every case of acute urethritis by urethral dilatation appears to me unacceptable. In urinary, as in general surgery, it is impossible to systematize the treatment of a given disease. If in some cases of acute urethritis, dilatation is indicated as a therapeutic adjuvant, it is the exception which I have never met. In my opinion it would be dangerous to spread broadcast without modification the therapeutic method proposed by Dr. Le Fur.

Drs. Janet, Pillet and Noguès favor the opinions expressed by Dr. Minet concerning the dangers of dilatations and in general the introduction of any instrument into an acutely infected urethra.

Dr. Le Fur in reply to the criticisms which have been made in regard to dilatation in the treatment of gonorrhea states that he has been misunderstood. He has never advised dilatation of the canal in acute gonorrhea but only in subacute and chronic cases. Instead of continuing indefinitely urethro-vesical irrigations in a rebellious case of gonorrhea,

he advises the combination of dilatation and irrigation as soon as pain and acute inflammation have disappeared, that is to say, at the end of three weeks or a month. At that time there is no longer suppuration of the entire canal but it is localized at certain points, either on the surface as ulcerations or deeper as in interstitial or glandular urethritis. Dilatation then acts in the manner of an intraurethral massage. Cautiously performed with soft bougies from 16 to 25 French and following a urethro-vesical irrigation with permanganate of 1 to 4,000 strength, even in cases where there are still gonococci in the discharge, indicating a glandular localization of the organism, it offers no difficulties and frequently shortens very markedly the course of these rebellious cases. The author points out that this method has moreover another great advantage, namely that of preventing stricture.

B). URINARY LITHIASIS IN THE ARMY

Dr. Cathelin shows the relative frequency of urinary calculus during the war in soldiers of middle age. He observed 41 cases in the Urological Center of the 5th district. He saw 20 cases of renal calculus but operated upon only 6, 2 by "Kystolithotomy," a technique permitting one to determine the presence of a serous cyst or abscess on the surface of the kidney or at one of the poles, which greatly simplifies the operation. He has seen several cases of calculus of the pelvic portion of the ureter which he believes should not generally be treated by uretero-lithotomy, as they frequently are relieved by auxillary methods. He operated upon 13 cases of vesical calculus, 10 by means of the lithotrite and 3 by suprapubic cystostomy which requires special indications.

He has treated several cases of calculus lodged in the urethra which are usually easily handled. In conclusion he insists upon the military necessity of making compulsory such methods as radiography, cystoscopy and ureteral catheterization which are indispensable to diagnostic accuracy and treatment.

Dr. Pillet attached to the Urological Center at Rouen performed 4 pyelotomies, 3 nephrectomies, 3 nephrotomies, 8 lithotripsies, 2 suprapubic cystotomies, and 1 prostatectomy for calculus. He calls attention emphatically to two points: (1) The advisability of delaying surgical intervention in every case in which the diagnosis is uncertain. The patient should be observed carefully and at the least pretext, metallic exploration or better still cystoscopy should be employed. In suspect-

ing renal calculus, radiography should be abundantly used. (2) The danger of mistaking calculus for other conditions presenting similar symptoms.

Dr. Reynès reported the case of a soldier aged thirty from whom two vesical calculi, weighing 130 grams were removed. This patient had had symptoms for twenty years which had exempted him from military service. During the war he was sent into the army as an artillery observer but was soon discharged with the diagnosis of incontinence. In reality he had paradoxical incontinence, the calculus having almost completely obstructed the vesical neck. It is interesting that this patient had been accused repeatedly of malingering and threatened with military discipline.

Dr. Pasteau observed that urinary calculi which are rare as a rule in soldiers on active service have become more frequent during this war. He suggests, as an explanation of this fact, the hygienic condition brought on by the war and the wounds and secondary infections of the urinary tract. The diagnosis of calculus is not especially difficult. In order to avoid regrettable errors, it is well to remember that calculus may exist without symptoms—the so called latent calculus—and patients in whom diagnosis is uncertain should be referred to the genito-urinary service. Every method of diagnosis, namely cystoscopy and radiography, should be employed in these conditions for these offer every security to the patient as well as to the surgeon and insure appropriate treatment.

Dr. Le Fur has observed a large number of vesical calculi developing about débris in wounds which involve the bladder and are associated with lesions of the neighboring bones. He has operated upon almost all of these cases by lithotripsy, rarely by suprapubic incision, reserving the latter method of attack for those cases presenting lesions of the urethra or bladder which would prevent the use of the lithotrite. He had also observed calculi developing about drains employed in perineal and urethral wounds which have passed into the bladder through the posterior urethra. He has also seen several cases of renal lithiasis following wounds. A first group is composed of those in which numerous small renal calculi are formed and expelled with or without colic. At times they are of fair size complicating wounds of long standing, as for example a wound of the urethra and bladder with fracture of the pelvis. These

calculi may be either phosphatic in which case they are usually secondary to an ascending renal infection or they may be composed of any of the urinary salts. Large renal calculi which the author has observed in patients with long standing wounds fall into two groups: (1) Two cases of unilateral lithiasis in soldiers who developed hematuria and violent lumbar pain following the explosion of a shell and in whom a renal calculus was found two or three years after the trauma. These 2 cases suggest the interesting question of the relation of renal traumatism to renal lithiasis. (2) Bilateral renal lithiasis in those wounds in the lower urinary passages. Of these there were 2 cases of wounds involving the urethra, one of which was treated successfully by a circular urethrorrhaphy. Both of them developed subsequently pyuria with ascending renal infection which was complicated by bilateral renal lithiasis. Nephrotomy was performed first in each case on the functionally better kidney. In one of the patients death in uremia resulted in five days and the autopsy revealed an extensive phlegmon of the operated kidney, while the other kidney was totally destroyed and its ureter completely obstructed by two calculi. The second patient survived a nephrotomy of the better kidney with extraction of all the calculi. Four months later the opposite kidney which was completely destroyed as a result of calculus obstruction of the ureter was removed. The patient was completely cured.

Dr. F. Legueu discusses especially urinary calculi in connection with wounds. He places special emphasis on vesical calculi which occur very frequently after wounds of the organ. These calculi which appear to be associated with inflammatory conditions of the bladder oftentimes occur after a very trivial lesion which is concealed and difficult to discover. This may be the result of an injury involving the bladder and the bony pelvis. A fistulous tract may open into the bladder and persist for a long time after the closure of the external wound. From time to time small portions of bone breaking off are discharged into the bladder and form the nuclei of future calculi. The lesion is easily recognisable by cystoscopy and the existence of osteopathic fistulae has been demonstrated several times by operation. Their surgical cure by excision of the fistulous tract is not to be recommended as it involves too extensive a dissection. It is far better to remove the calculus with the lithotrite and wait for the spontaneous healing of the fistula.

Dr. G. Vincent presented to the urological association several observations on vesical calculi removed from soldiers discharged from the army

and demonstrated large stones which were removed by incision. He followed this with consideration of the influence of conditions of army life on the development of urinary calculi.

Dr. Escat: Of 2914 hospital cases in the Urological Center of the 15th district, there were 60 cases of renal, ureteral and vesical calculi. Fifty-four required surgical intervention, 6 pyelotomy, 1 uretero-lithotomy, 14 nephrotomy, 13 nephrectomy and 20 lithotripsy. In this number are included cases of lithiasis secondary to wounds of the urinary tract. In some cases the routine and hygienic conditions of the hospital appear to have some influence on the production of oxalate and urate calculi in those severely wounded, while in others fatigue and general conditions of army life have aggravated renal lithiasis which previously had been well tolerated or unrecognised. This latter group was treated as follows: 6 by pyelotomy, 14 by nephrotomy, 1 by uretero-lithotomy and 13 by nephrectomy. Vesical calculus has been treated by lithotripsy. As is usual in times of peace, large renal calculi in cases of pyelonephritis of long standing have been well tolerated over a long period and well compatible with the fatigue of army duty. Radiography alone has revealed their presence. Calculus in the renal pelvis has been well tolerated among officers who continued on duty without being operated upon. However it is evident that in patients with renal calculus who have rendered service, the state is under obligations to provide appropriate treatment. Pyelotomy and nephrotomy produce a complete cure, while nephrectomy mutilates. Nephrectomy should be considered only in serious cases. It produces permanent invalidism, and at times low function of the remaining kidney. As a general rule the reformation of a calculus, owing to the existing nephritis, requires a nephrectomy.

Dr. Desnos reported a case of the formation of renal calculi following a wound of the ureter. This patient was wounded in September, 1915, the bullet entering near the sacrum and emerging in the hypogastric region. During its course the pelvis was fractured, the ureter torn and the peritoneum perforated, the last condition being treated immediately. Besides the bladder which remained open there persisted a suppurating wound of considerable size into which the lower end of the torn ureter discharged urine. The wound healed at the end of a year at which time there appeared symptoms of ureteral obstruction with phenomena of intermittent pyonephrosis. The urine remained very purulent and at the end of six months a very severe attack of renal colic was

followed by the expulsion of a large calculus through the ureter, thus demonstrating the absence of ureteral stricture. Owing to the repeated passages of calculi and the persistence of fever, a nephrectomy was performed. The kidney presented numerous cavities, each containing a phosphatic calculus. An extensive war injury may thus result in a large infected wound which involves the ureter without producing its obliteration. It is noteworthy that as long as the wound remained open signs of retention did not develop, appearing only when the normal ureteral meatus began to function. The rapid development of numerous intra-renal calculi, some having no communication with the pelvis, is likewise remarkable.

C). TRAUMATIC LESIONS OF THE POSTERIOR URETHRA

Dr. Heitz-Boyer. The treatment of traumatic lesions of the posterior urethra will depend upon whether they are simple or complicated with other lesions, either visceral or osseous. In the first place, in uncomplicated lesions of the urethra, the soft parts should receive the same consideration as the urethra itself. The treatment of the soft parts consists in excising the injured tissues, immediate suture being delayed in the majority of cases especially when the lesions are in the region of the buttocks. The treatment of the urethra varies according with the case. If the lesions are recent and not extensive immediate suture over a sound in the urethra should be attempted. If the lesions are very extensive and of longer than forty-eight hours duration, it is better to leave the urethral wound open and institute suprapubic drainage, the latter being particularly indicated in prostatic lesions. The treatment of lesions complicating the urethra and rectum only rarely permits of immediate suture and in these instances it is better to resort to colostomy and perineal urethrostomy. In cases complicated by vesical lesions, suprapubic cystostomy is always necessary while the coexistence of bony lesions requires the careful removal of fragments and drainage.

Dr. Marion concludes that in the presence of an obstruction of the posterior urethra following traumatism, it is necessary to search for the two ends of the canal, to resect the interposing tissue and to reconstruct the urethra by an end to end anastomosis. If the latter is not possible, the periurethral tissues should be approximated. In an end to end anastomosis it is not advisable to introduce a sound into the urethra but in case the reconstruction is attempted by approximating the peri-

urethral tissues a sound should be used. It is of advantage also to allow a filiform to remain in the urethra as this greatly facilitates the future passage of instruments for dilatation. In case of a stricture developing at the site of anastomosis dilatations should be carried out and in the event of their being unsuccessful an internal urethrotomy should be performed.

The treatment of fistulae complicating lesions of the posterior urethra varies considerably with the case. After performing a cystostomy to divert urinary drainage, the fistulous tracts should be excised, abscesses opened and foreign bodies, such as calculi and sequestra removed. Following this, urethral dilatations with a sound often accomplish a cure. In cases where this procedure proves unsuccessful and where the urethra is impermeable, it is necessary first to find the urethra and then to reconstruct it in a manner varying with the lesions. In any case it will be necessary to continue suprapubic drainage for some time until a cure is obtained.

In the treatment of urethro-rectal fistulae one of several procedures may be employed. Having separated the urethra from the rectum, the urethral and rectal orifices of the fistula may be closed separately after which the periurethral tissue should be interposed between them. In certain cases it may be advisable to free the rectal mucosa containing the fistulous opening and amputate it as in the Whitehead operation for hemorrhoids, after which the free edge is brought down and sutured to the skin.

In cases in which there has been extensive destruction of the urethra and perineal tissues, it may be possible to employ plastic methods, utilizing the serotal tissue or skin from the thigh. There are however certain lesions which are beyond the resources of surgery. Total destruction of the posterior urethra which is sometimes complicated by destruction of the anus may be treated by suprapubic cystostomy, perineal urethrostomy and if the rectal lesions are irreparable, by the formation of an artificial anus.

There are certain cases in which, after all the wounds are healed, the patient still has urinary difficulty. It is well in these cases to bear in mind the possibility of periurethral abscess due to a remaining shell fragment and to act accordingly.

Following the repair of the urethra systematic urethral dilatations are necessary in order to prevent stricture formation or deviation of the canal.

Finally in operating upon the posterior urethra, a good exposure is

necessary. Among the methods which accomplish this in the most satisfactory manner is the separation of the triangular ligament.

Dr. Escat has observed 24 cases with traumatic lesions of the posterior urethra; 17 times they have been associated with osseous lesions, 12 times with anal or ano-rectal lesions and in 8 cases the condition has been complicated with bladder injuries. Subsequently these lesions became modified by chronic infection and loss of tissue giving rise to fistulae and strictures. Traumatism affects either the prostatic or membranous urethra. When the posterior urethra is involved there occur (1) cavity formations; (2) foreign bodies, either free or fixed, as calculi or projectiles; (3) various urethral or epididymal fistulae which may simulate genital tuberculosis. Periosteal foci of infection may cause extensive infection in the region of the symphysis pubis; (4) deviations of the urethra. The posterior urethra, owing to the absence of spongy tissue is more apt to develop deviation than stricture.

In cases in which the membranous urethra is involved, the most important clinical type is characterized by associated lesions of the bulbous urethra which is either primarily involved or secondarily so by extension of the infection. The prognosis of lesions of the membranous urethra becomes more serious when there is a coexisting osseous lesion. The treatment of choice is suprapubic cystostomy combined with free perineal drainage. A long median incision beginning at the scroto-perineal junction is continued back to meet an inter-ischial incision. This gives an excellent exposure of the entire superficial perineum and facilitates the separation of the urethra and rectum. Unilateral or bilateral incision of the transverse muscles and the middle aponeurosis exposes completely the deep perineum and the ischio-rectal fossa. In the repair of the urethra the following points are worthy of emphasis. (1) having freed the bulb from the rectum it is carried backward in front of the membranous urethra where it is sutured. (2) In cases in which the superficial layers of the perineum have been destroyed, the scrotum which has been freed can be utilized to repair the defect.

Dr. Michon advises the immediate anastomosis of the two urethral ends in the less severe cases in order to facilitate surgical procedures which may be carried out subsequently. Suprapubic cystostomy is the rational procedure as it provides for urinary drainage and is easily handled postoperatively. He has never found it necessary to perform an iliac enterostomy and in avoiding pelvic cellulitis he prefers free perine-

cal incision for the drainage of the pelvis. The employment of a retention catheter in cases in which the urethra is sutured is not to be recommended. If subsequent difficulty in introducing instruments for the purpose of dilatation is anticipated, a filiform which can be used as a guide for future instrumentation can be left in the urethra.

Dr. Pasteur believes that in injuries to the posterior urethra it is necessary to make a large incision and if the condition of the patient permits, a careful exploration of this region. It is also necessary to insure free urinary drainage by performing a suprapubic cystostomy. The tissues adjacent to the urethra which have been injured either traumatically or as a result of operation should be drained also. The perineal layers should not be sutured and an attempt should be made to bring together the ends of the torn canal over a retention catheter. Subsequently free opening of the perineal area and the fistulous foci, aided by suprapubic cystostomy, is still the best means of avoiding and if necessary of treating stricture of the deep urethra whose prognosis is always serious.

Dr. Marsan has treated 7 cases of injuries involving the posterior urethra, 2 of which died on the day following operation, one of shock, the other of gas infection. Another died at the end of 6 weeks of septicemia. Four are well and 2 have complicating wounds of the rectum. The technique which he employed was as follows: (a) cleansing and drainage of the wounds of entrance and exit; (b) suprapubic cystostomy until a cure has been completely effected; (c) a perineal T incision (longitudinal and inter-ischial incisions) to expose the urethra, the two ends of which are approximated; (d) suture of the two ends at 4 points, the sutures including the periurethral tissues. A retention catheter is allowed to remain for three or four weeks; (e) suture of the rectal wounds; (f) free perineal drainage, the wound being left wide open; (g) removal of fragments in case of fracture of the pelvis.

Dr. Minet believes that there is too often a tendency to delay performing suprapubic cystostomy which should be carried out in every case of rupture of the bladder and of the prostatic and bulbomembranous portions of the urethra by a projectile. He emphasizes a case of rupture of the perineal urethra complicating a wound involving the ano-rectal and prostatic regions. Delayed healing presents the maximum of difficulty in cases of destruction of the so-called membranous urethra

where the complete excision of the scar tissue involves the loss of the external sphincter and where a wedge shaped incision, as practised by Dr. Minet, increases the possibility of the development of stricture.

Dr. Rochet agrees with the conclusions which have been formulated. He recognises the advantages of separation of the triangular ligament as pointed out by Dr. Marion, in order to explore and treat wounds of the posterior urethra. It further enables the operator, in cases of fractures of the ascending ramus of the ischium, to break up urethral adhesions and to discover bony fragments or foreign bodies. The importance and seriousness of ultimate results in these cases, as emphasized by Dr. Pasteur, are very interesting. The immediate result may be satisfactory but none can foresee the complications which may arise in the future which may necessitate further operative procedures. There are three classes of patients: (1) the cases in which the cure is permanent requiring but two or three annual courses of urethral dilatations; (2) cases in which a second operation will be necessary to accomplish the desired result; (3) unfavorable cases with repeated recurrences of dysuria, abscess formation and fistulae and which eventually require either a perineal urethrostomy or a suprapubic cystostomy which insures a life of invalidism.

Dr. Le Fur in 52 cases of wounds of the urethra has observed 40 cases in which the posterior urethra was involved, in 19 of which there was a complicating fracture of the pelvis. The treatment of these injuries varies according to the case. Often enough the operator is content to allow cicatrization to occur around a retention catheter. In these cases a certain number of strictures of the membranous urethra develop but the author has never observed stricture formation in the prostatic portion of the tract. In the prostatic urethra he has seen deviation and occasionally irregularities which require catheterization. In 2 cases the approximation of the periurethral tissues over a retention catheter gave a satisfactory result.

Secondary suture was necessary in a total of 6 cases, resulting in 2 successes and 4 failures. Of the later, 2 cases were infected and 2 uninfected but in all of them there was considerable loss of tissue and recurring hemorrhages with the formation of perineal hematomata. It is better in these cases not to unite tissues which are badly injured but to provide free perineal drainage.

In cases of persistent perineal fistula urethroplasty is almost always

successful. In about 50 per cent of the cases where the membranous urethra is involved this operation is followed by slight stricture formation.

Suprapubic cystostomy is always indicated and is a large factor in final cure. The association of osseous lesions (fractures of the pelvis and osteitis) in general makes the prognosis more uncertain and renders cure of the urethral lesions more difficult. When osseous lesions complicate urethral wounds, it is necessary to remove all fragments of bone and areas of osseous infection; indeed a cure of these lesions should always precede operations on the urethra.

Urethro-rectal wounds and secondary fistulae are very rebellious lesions and their cure is very difficult in contrast to rectovesical fistulae as shows by Legueu. The proper operation in such cases consists in isolating the two orifices and careful separation of the communicating tracts, either by ligature in case of a narrow tract, or by separate suture of the two orifices, rectal and urethral, when the tract is larger. In some cases the drawing down of the entire rectal wall or the mucosa have yielded some results while in others lateral displacement or torsion of the rectum has been successful.

Colostomy should never be performed immediately on arrival of the wounded; indeed it is only required in exceptional cases. In every case but one a cure has been effected without its employment.

D). SIMULATIONS OF URINARY DISORDERS AMONG SOLDIERS

Dr. J. Janet: Simulation of diseases of the urinary passages is rare among soldiers. Fever at times is pretended but the taking of the temperature will dispose of this. Occasionally hematuria is the complaint but unexpected examination avoids the error. Gonorrhea is occasionally simulated by the introductions of soap or Panama wool into the urethra. It may however be contracted purposely by intercourse with a woman known to be infected or the urethra may be inoculated with the pus from another soldier. Gonorrheal arthritis may be feigned by energetic friction of the knee and pretended pain on movement. Dr. Eteau has reported a case of urethral stricture following the introduction of absorbent cotton into the canal. Vesical retention may be simulated by incomplete micturition, an interesting case of which has been reported by Dr. Escat. Incontinence of urine is simulated less frequently than one would believe. Dr. Eteau detects these cases by making a manometric determination of the force of the bladder

musculature and a dynamometric determination of the contractility of the sphincter and by ascertaining the frequency of nocturnal voiding. Albuminuria is feigned by the addition of albuminous substances to the urine or by the injection of egg albumin into the bladder. The chemical nature of egg albumin or observation of the patient makes possible the detection of this fluid. Polyuria is sometimes claimed by soldiers who have added water or the urine of others to their own. Observation at the time of voiding suffices to dispel any doubt. To detect pretended anuria the patient may be given 5 grams of urea to see whether it is recovered in the urine. Examination of the specific gravity of the urine which should decrease as the amount increases is also a means of detecting this simulation.

Dr. Escat: Urinary disease is difficult to simulate and unexpected examination frequently reveals the fraud. Malingering of this type is rare, occurring in only 7 out of 3,000 hospital cases with urinary disorders. It is necessary to distinguish those who exaggerate minor symptoms. There are many urinary neurasthenics who besiege physicians with demands for consultations in war time as well as in peace. These cases have nothing in common with the malingerer. The physician should analyze with the greatest care the alleged functional symptoms, systematic exploration of the genito-urinary symptoms as well as careful physical examination being necessary before concluding that a symptom without appreciable cause is feigned. The frequency of pretended urinary incontinence has been greatly exaggerated. There are unquestionably cases of what might be termed "essential" incontinence of urine, either continuous or reappearing from time to time while in active service, an incontinence dependent upon the strain of military duty. The 7 cases of simulation the author has observed comprise one of incomplete pseudo-retention, 2 of pseudo-albuminuria and 4 of pseudo-hematuria. In cases of retention it is necessary to consider the factor of excitement. The 2 cases of pseudo-albuminuria resorted to the injection of egg albumin and milk into the bladder. In considering the cases of false hematuria the injection of picric acid to give an abnormal color to the urine should be emphasized. In every case of simulation the author has exhausted every means of urological and medical investigation and has consulted neurologists and chemists. He emphasizes the necessity of compelling the patient to urinate in the presence of the physician and the value of unexpected passing of the catheter. The injection of irritating or harmless substances, either gas or liquid, or of water in amounts

unknown to the patient readily reveals the pretention of incomplete retention. The injection of titrated solution of glucose is equally effective in determining whether the patient has urinated within a given period and if he has added other urine to his own.

Dr. Eteau: Among 32 cases of urinary retention observed over a period of 32 months, 18 without apparently anatomical cause were to be classed under the name of "atonic retention." Is it a case of pure simulation or may it have been originally a case of simulation which resulted in such intravesical tension with subsequent development of deficiency and diminished contractility as in the overworked heart? Is it a question in other cases of inhibitory phenomena resulting from nervous excitation? By dynamometric methods it is possible to determine the integrity of the sphincter. On the other hand manometric determinations have demonstrated insufficient tonicity of the bladder musculature (cause or effect of retention). Inasmuch as retention is an early sign in neurological diseases, especially in tabes, it is necessary to examine the reflexes, to determine the Wassermann reaction and to cystoscope the patient. In every case extreme caution should be observed in making a diagnosis of pure simulation. The question deserves further study.

Dr. Minet recalls that in 1915 he suggested the employment of a retention catheter for detecting simulation of albuminuria.

Dr. Genouville demands that patients, who having been treated in a certain service are suspected of simulation, should wherever possible be hospitalized in the same service so that the records of the cases may be available.

A CASE OF URINARY OBSTRUCTION DUE TO ENLARGEMENT OF THE ANTERIOR PROSTATIC LOBE

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The occurrence of tumor formations of either fibrous or adenomatous nature, which involve the anterior prostatic lobe to the exclusion of the rest of the prostate must be exceedingly rare. A survey of the literature fails to reveal any reported cases of this condition which had been diagnosed clinically and removed. Wade (1) reported a case of solid tumor of the anterior lobe but his material was obtained at autopsy, the case having died without operation. H. Thompson (2) reviewing 125 cases of prostatic hypertrophy reports 3 cases in which there was an isolated hypertrophy of the anterior commissure. A cyst of the anterior prostatic commissure was reported by Abbe (3).

It is of interest in this connection to review in brief the embryology of this region. Lowsley (4) in his comprehensive studies on the embryology of the prostate describes five groups of tubules growing out from the posterior urethra at about the 12th week of intrauterine life. They spring from the urethral floor beneath the ejaculatory ducts and the bladder, from the prostatic furrows, from the floor of the urethra beyond the ejaculatory ducts and from the anterior urethral wall forming respectively the median, lateral, posterior and anterior prostatic lobes. The anterior lobe tubules are relatively few in number and in the thirteen weeks fetus average about 12, 8 being paired while 4 spring directly from the mid line. These tubules however fail to keep pace with the development of the other prostatic lobes and at the twenty-second week they show definite signs of atrophy. At the thirtieth week these anterior tubules have shrunk still further in size and their number has been diminished by one-half. Thus

in the specimen studied there were but 8 small branching tubules communicating with the anterior urethral wall. This degenerative process continues until birth, at which time the anterior lobe consists of but 2 small branching tubules which open upon the ventral wall of the prostatic urethra at its mid portion.

Among 93 specimens of prostates studied by Lowsley (4) 2 were found having hypertrophied anterior lobes. Legueu (5) reporting 500 cases found only 3 instances of anterior lobe hypertrophy and Alexander Randall in a personal communication states that he has yet to find such a case in his extensive autopsy studies of contracture of the vesical neck.

The following case of anterior lobe enlargement causing urinary obstruction is believed to be of sufficient interest to warrant its report in detail. This patient, aged twenty-seven, was seen in May, 1917. He gave a history of gonorrhea contracted nine years before and a year later suffered from marked urinary frequency which lasted for four or five weeks, then clearing up spontaneously. About a year later he had another attack of vesical irritability and was treated by urethral dilatations for a supposed stricture of the urethra. This instrumentation was followed by complete urinary retention. He was catheterized for a week at the end of which time an external urethrotomy was performed and urinary drainage through a perineal tube continued for several weeks. This was followed by no symptomatic improvement.

Cystoscopy July 1, 1917, showed 100 cc. of very purulent residual urine. Study of the prostatic orifice revealed a tumor mass springing anteriorly and occupying about one-fourth of its circumference. It was smooth, rounded and was apparently of the size of the distal phalanx of the little finger. It was apparently sessile and the mucous membrane covering it was smooth and only slightly inflamed. The bladder wall showed changes typical of long standing obstruction. There was marked hypertrophy of the interureteral bar and basal formation. Ureteral catheterization revealed a double pyelitis, both urines containing pus and staphylococcus albus. This promptly cleared up with lavage with 1 per cent silver nitrate.

At operation on December 10, 1917, the bladder was opened suprapubically. Springing from the anterior aspect of the prostatic orifice and extending for some distance into the urethra was a mass measuring 1.5 by 1 by 1 cm. The normal looking mucosa which covered it was incised transversely and the mass removed. A catheter was introduced per urethram and the bladder closed. On examination three months later there was no residual urine.

On section the specimen removed is composed largely of fibrous tissue and smooth muscle. There are several gland elements which resemble normal prostatic tissue and the larger ducts are quite dilated. At no point however is the picture even suggestive of adenoma.

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KIDNEY FUNCTION IN DISEASE

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INTRODUCTORY

The improvements in the methods of blood examination in recent years have taught us a good many facts regarding the presence in the blood in health and disease of many substances such as urea, uric acid, creatinin and the total non-protein nitrogen. Various tests of kidney function have gradually taken their place among the methods of diagnosis of kidney disease. Yet in spite of all the work done there is a great deal of chaos in the common understanding of the kidney function in health and disease. This is made especially evident by various papers on war nephritis which have appeared lately and by the continual search for adequate functional tests.

This paper attempts an understanding of kidney function in disease and an explanation of the symptoms involved, basing such attempt on the *modern theory* of kidney secretion and on the facts of kidney pathology so far known.

NORMAL KIDNEY FUNCTION

In his recent work on the Secretion of Urine, Cushny gives a lucid exposition of what he calls the *modern theory* of kidney secretion. In main it assumes glomerular filtration and tubular reabsorption. The function of the glomeruli is to filter through a semi-permeable membrane, Bowman's capsule, a deproteinized plasma. The energy supplied by the blood pressure is normally of a sufficient degree to cause filtration. The filtering fluid is the blood with which the kidney is remarkably well supplied. Cushny calculates that the whole of the blood passes through the kidneys in about five minutes. The kidney vessels

have in their vasomotor nerves a regulating mechanism which is very sensitive to reflex stimuli. The resulting filtrate contains all the soluble constituents of the blood, with the exception of the colloid substances, to the large molecules of which Bowman's capsule is impermeable. Filtration through Bowman's capsule like filtration through any other membrane depends on:

- (1) The difference in pressure on the two sides of the membrane;
- (2) The character of the membrane. Changes in the character of the membrane may alter its permeability, as for instance, insufficient oxygen supply increases resistance to permeation.
- (3) The nature of the filtering fluid. The colloids of the plasma which are not permeable exert in proportion to their concentration an osmotic pressure which retards filtration.

The function of the tubules is to concentrate the fluid received from the capsule so as to preserve the water and certain salts for the body economy. These substances Cushny calls *threshold bodies* because they are only excreted when they exceed a certain threshold value in the blood, while others which are excreted in proportion to their absolute values in the blood are not absorbed by the tubules but escape by the ureters. The tubules absorb sodium, potassium, calcium, chloride and dextrose, in about the proportion contained in Locke's fluid, and a minute amount of uric acid. The excess of the threshold bodies, together with the non-threshold bodies, such as urea, sulphates, and foreign substances, none of which is absorbed by the tubules, pass on to the ureters. Non-absorbable substances limit absorption of water by exerting osmotic pressure, and "the urine can, therefore never exceed a certain concentration at which the osmotic resistance is equal to the power of absorption."

The evidence for the *modern theory*, as well as the refutation of the older theories must be read in Cushny's work and is well worthy of study. The one apriori consideration that is worthy of notice is that the kidney, though hitherto supposed to be a secretory gland, has unlike every other secreting gland of the body no secretory nerve supply or any other nerve supply except vaso-motor, contractor and dilator fibers. Search for vagus connection as well as for secretory nerve fibre has been fruitless.

The reader is referred to Gaskell's work on the Sympathetic Nervous System for evidence and literature.

The action of diuretics can well be explained by the *modern theory*. Aside from those drugs whose action improves the circulation or dilates the kidney vessels, the action of the most efficient diuretics, the xanthine compounds, may well be explained by their being non-threshold bodies. These are not reabsorbed in the urinary tubules and by their osmotic resistance prevent water absorption and thus increase the urinary flow.

The *modern theory*, aside from its probable intrinsic truth, as will be seen further on, is of great practical value.

The question we have to answer for ourselves now, is: How is the function of filtration and reabsorption maintained when the kidney is diseased?

THE COMPENSATORY MECHANISM

Manifestly any diseased state of the kidney can only have effect on its function in so far as it causes damage to a sufficient number of glomeruli or to a sufficient number of tubules, in the first case impeding filtration, in the second diminishing absorption. Any affection which, though involving part of the kidney, still allows practically complete filtration by the rest of the kidney does not call for any extra mechanism on the part of the body. In acute affections the function of the tubules is never completely abolished and there is always some absorption; in chronic affections the condition of the tubules is nearly always secondary to that of the glomeruli. The primary factor in diseases of the kidney is the function of the glomeruli, the function of filtration. As soon as enough glomeruli have been involved to make filtration difficult, another factor is called upon to increase filtration. This cannot be accomplished by increasing secretion of the tubules, for the tubules do not secrete, nor are any nerves present which could stimulate them to secretion. The only mechanism which the body has at its command is that of increasing the pressure in the filter. This is actually what happens. Increase of pressure is slight if this will overcome resistance and

result in filtration; pressure may reach extreme degrees if in this way only resistance can be overcome and filtration result. The mechanism will be inadequate if the highest possible pressure does not result in complete filtration. Likewise, if the increased pressure fails for some other reason, insufficient filtration will result leading to uremia and finally death.

When we consider carefully the mechanism of the kidney it gradually becomes clear that we must regard the kidney more and more as a mechanical filter rather than a secretory organ. As in a mechanical filter the stoppage of pores requires increased pressure for continued filtration, so it is with the kidney. But the kidneys are so situated and their blood supply is such, that increase in blood pressure in the kidney vessels is impossible without an increase in pressure in the whole arterial system. We may speak of this increase in pressure in glomerular disease as *the compensatory mechanism of hypertension*, and it is an essential point in considering kidney function in glomerular disease.

So much for tubules and glomeruli. There is one other element which calls for the compensatory mechanism of hypertension and that is thickening and intimal changes in the small and smallest arterioles of the kidney. Such changes throughout the kidney would, by diminishing the blood supply to, and the pressure in, the vasa afferentia, decrease filtration in the glomeruli, though the glomeruli themselves are not diseased. This will therefore call for compensation by means of increased pressure to force sufficient blood through the thickened arterioles.

CLASSIFICATION OF NEPHROPATHIES

In considering the function of the kidney in diseased states classification is of course essential. Classification of kidney disease has recently been attempted on the basis of functional response to certain tests. Nearly all of these tests and classifications were based on the assumption that certain parts of the kidney excrete certain substances and failure to excrete these substances indicates disease of that part of the kidney. If we hold to the *modern theory* of kidney secretion such assumption is

of course untenable. Classification of diseased states, when impossible on an etiological basis, must be based on definite anatomical changes when these are present. In kidney disease we have gradually learned that the glomeruli, tubules and vessels, when diseased, will each produce characteristic symptoms, and classification into glomerular, tubular and vascular affections is of course natural. Volhard recognized this long ago and in a lecture delivered in 1911 proposed a classification, which he and Fahr elaborated in their work on Bright's disease published in 1914. Although gaining recognition this work on Bright's disease is a good example of how an epoch-making contribution can be neglected and passed over by investigators who should be familiar with the current literature in their special field.

The classification of nephropathies of Volhard and Fahr should do away with every other classification and is as follows:

A. Degenerative diseases: Nephrosis, genuine and of known etiology, with and without amyloid degeneration of the vessels.

1. Acute course.
2. Chronic course.
3. End stage: Nephrotic contracted kidney without increased blood pressure.

Subclass: Necrotic nephroses.

B. Inflammatory diseases: Nephritides.

1. Diffuse glomerulo-nephritis, with obligatory increased blood pressure.

Course in three stages:

- | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> 1. The acute stage 2. The chronic stage, without kidney insufficiency 3. The end stage, with kidney insufficiency | } | All three stages may run their course: (a) without nephrotic admixture; (b) with nephrotic admixture; i.e., with marked and diffuse degeneration of tubular epithelium (mixed form) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

2. Focal nephritis, without increase in blood pressure:

(a) Focal glomerulo-nephritis:

1. Acute stage.
2. Chronic stage.

(b) Septic interstitial focal nephritis.

(c) Embolic focal nephritis.

C. Arterio-sclerotic diseases: Scleroses.

1. The bland, benign hypertension = pure sclerosis of the kidney vessels.
2. The combined form: Malignant genuine contracted kidney.—sclerosis plus nephritis.

FUNCTION IN NEPHROSIS OR TUBULAR DEGENERATIVE DISEASES

Lesions of the tubules are of a degenerative character and involve a single row of tubular cells without any exudat  in the surrounding tissue. The term nephritis is really not justifiable in this condition although some pathologists persist in using it. The term tubular degeneration is much more exact and recently the term nephrosis has been proposed for it. In considering kidney function in tubular degeneration, we must not forget that Bowman's capsule is the beginning of the uriniferous tubule and that the part of the capsule in apposition to the glomerular tuft is just as much involved in tubular lesions as the convoluted tubules, although the glomerular tuft itself is entirely intact and does not show involvement at all. Part of the urinary symptoms must be ascribed to involvement of the capsular layer of cells.

Let us now consider kidney function in acute tubular involvement. The glomeruli are not involved and filtration proceeds therefore as in the normal kidney. There is no need then of the compensatory mechanism of hypertension and the blood shows a normal level of non-protein nitrogen and of urea. Absorption although somewhat reduced in severe cases is to a great extent still present, for the tubules are not destroyed throughout their whole length but only in areas, and a high degree of absorption is always possible. The function of the kidney is therefore hardly disturbed and such dyes as phenolsulphonephthalein are excreted in normal proportion. There is no increase in tension and no functional insufficiency.

The symptoms of acute tubular degeneration are: Albuminuria and cylindruria, ranging from very little to very large amounts; edema, anasarca and cavity hydrops of varying amounts.

An explanation of these symptoms is necessary. The albumin appearing in the urine has been shown to be derived from the

blood. It has further been shown that the albumin passes through the glomerular capsule. The reasonable assumption would therefore be that the glomerular capsule which is injured with the rest of the tubules, becomes permeable to the colloid constituents of the plasma. These passing through the capsule become concentrated with the rest of the plasma constituents on their way downward, and as they become concentrated a part of the albumen solidifies and forms the ground substance for casts. Upon these, cellular debris from the injured tubules is deposited. As the glomeruli themselves are not injured, and as therefore no blood leaves the capillary tuft, no blood appears in the urine.

We have more difficulty in explaining the accompanying edema and cavity hydrops. We can only assume that the toxin responsible for the tubular degeneration also injures the endothelial layer of the body cavity and of the capillaries in the subcutaneous tissue, allowing for the passage of the transudate, which for unknown reasons is rich in lipoids. As the transudate like all other fluids in the body contains sodium chloride in the same proportion as the blood, the sodium chloride in the urine is therefore reduced.

The etiological problem is not yet solved. It occurs after prolonged suppuration, in early syphilis, in tuberculosis and in the course of various infectious diseases, often without any apparent cause. The presence of amyloid in the kidney and various other organs may complicate but it does not change the kidney picture.

FUNCTION IN THE SUBLIMATE KIDNEY

The very mild form of the sublimate kidney is that of tubular degeneration or nephrosis, and the symptoms as well as the kidney function in this condition correspond to the description above. The severe form is an example of the subclass *necrotic nephrosis*. There is death of the tubular cells and casts of whole sections of the tubules appear in the urine. The glomeruli are not involved and function is the same as in the milder form, unless complicated by reflex constriction of the kidney vessels resulting in anuria. When this happens the picture changes

entirely. By means of the compensatory mechanism of hypertension an attempt is made to force blood into the glomeruli. If this does not succeed, the rest-nitrogen level in the blood gradually rises to a degree where, if no improvement sets in, death results. When with improvement, the vessels relax and the glomeruli again receive sufficient blood, hypertension and rest-nitrogen level soon fall to normal, and with regeneration of the tubular cells, the urinary picture gradually becomes normal.

FUNCTION IN ACUTE FOCAL GLOMERULO-NEPHRITIS

In tracing the function of the kidney through the various forms of glomerulo-nephritis it is best to begin with the focal nephritides in which the function of the kidney is least disturbed. In the focal nephritis occurring early in the course of a tonsilitis, the exanthemata or other infectious diseases, and in the embolic glomerulo-nephritis occurring in the course of streptococcus viridans endocarditis, only some of the glomeruli are affected in foci disseminated over the entire kidney. Not only are the numerous intact glomeruli able to carry on the function of filtration, but even the affected glomeruli have only a part of the capillary tuft inflamed and the rest is still able to functionate. The tubules being not at all affected or affected only in a mild degree, secondary to the glomeruli, the function of absorption is not disturbed. We have then in all the focal nephritides normal function of the kidney. Explanation is necessary for the symptoms appearing, namely, hematuria, albuminuria and cylindruria. Hematuria in Bright's disease always means glomerular inflammation with lesion of the part of the capsule just over the inflamed glomeruli. This allows the red blood corpuscles to get through with the blood plasma practically unfiltered.

We can of course understand that a focal nephritis of sufficient extent and a sufficient number of foci, may diminish the function of so many glomeruli that filtration will be impaired, and call for the compensatory mechanism of hypertension to produce filtration. Clinically such cases are rare.

FUNCTION IN THE FIRST OR ACUTE STAGE OF DIFFUSE GLOMERULO-
NEPHRITIS

The acute stage of diffuse glomerulo-nephritis is characterized pathologically by a swelling of the glomeruli with cellular proliferation in its mildest form, increasing to the formation of demilunes in the most severe form. All the glomeruli are diffusely diseased, some more and some less; some only swollen to a mild degree, still allowing the blood to pass through the capillaries of the tuft, others completely bloodless and impassable. The tubules show degeneration but their lesion is secondary to that of the glomeruli, and of minor importance. The capsular layer is injured whenever the glomerulus underneath is injured, for diminution of nutrition is sufficient to change its permeability, and as the blood that reaches the tubules passes first through the glomeruli, diminished blood flow through the glomeruli would of course also mean diminished blood supply to the tubules. This may in part be responsible for the amount of tubular degeneration present.

Tubular degeneration will of course show itself by the presence of marked albuminuria and the presence of edema and cavity hydrops. Glomerular inflammation shows itself by the presence of blood in the urine. But while in the focal nephritides the rest of the kidney is sufficient to maintain function, this is not so in the diffuse form where practically all the glomeruli are involved. How then is the kidney to maintain its function? As we have explained above, the only thing that the body can do is to increase the pressure so as to force blood through the affected glomeruli. That this is actually the case can be seen when we follow patients with acute diffuse glomerulo-nephritis, who previously have had normal blood pressures. With the onset of the nephritis there appear the urinary symptoms mentioned, the total urinary output is diminished and the blood pressure rises. The rise in blood pressure may only be 30 or 40 mm. of mercury above the normal. The calling into action of the compensatory mechanism of hypertension results in some filtration and some urinary output. But is the amount of filtration sufficient for the needs of the body?

The answer to this question we get at once on examining the blood for the amount of non-protein nitrogen. If filtration with the aid of hypertension is sufficient, the normal rest nitrogen level is about 25 to 30 mgm. per 100 cc. of blood. If not sufficient the rest nitrogen level is increased in proportion to the severity of the inflammation and in proportion to the inability to force filtration in spite of the increased blood pressure. Blood pressure of about 200 mm. and a rest nitrogen level of 100 mgm. per 100 cc. of blood are not at all uncommon in the acute stage of the severe forms of diffuse glomerulo-nephritis.

The behavior of injected dyes, which are non-threshold bodies, is like that of urea, which is a normal non-threshold body of the blood, and their excretion is diminished in proportion to the severity of the inflammation.

The inflammation may progress to an extent where all possible increase in blood pressure is of no avail in forcing blood through the glomeruli, so that filtration all but ceases and the rest nitrogen level gradually rises. Figures as high as 500 mgm. per 100 cc. of blood have been reported. As the rest nitrogen gradually increases symptoms of poisoning of nerve centres manifest themselves in drowsiness, stupor, jerking of tendons and increased reflexes, and death results. This is usually the case when the rest nitrogen level reaches a point above 200 mgm. per 100 cc. of blood. In inflammation where the rest nitrogen does not reach above this level, recovery is possible, and in figures below 100 mgm. it nearly always occurs. As the inflammation recedes filtration gradually becomes possible with lessened pressure. The urinary signs of hematuria and albuminuria are the first to disappear. The rest nitrogen gradually drops to a normal level with the blood pressure still increased and only when complete filtration is possible does the blood pressure return to normal.

Urinary symptoms, blood pressure readings and rest-nitrogen estimation give us at any time during the course of the acute stage of diffuse glomerulo-nephritis a survey of the functional capacity of the kidney.

FUNCTION IN THE SECOND OR CHRONIC STAGE WITHOUT KIDNEY INSUFFICIENCY

We have said above that the end result of the acute stage of diffuse nephritis is either recovery or death. There is another result in which the acute inflammation subsides and gradually enters a chronic stage. The glomeruli may recover in various degrees, with retention of glomerular substance sufficient for the purpose of filtration. That this filtration is sufficient for the needs of the body is evidenced by the normal level of rest nitrogen in the blood, yet this is only possible by means of the compensatory mechanism of hypertension. Cases in the second or chronic stage of diffuse glomerulo-nephritis show therefore a persistent hypertension, usually around 200 mm. of mercury and above, and a normal rest nitrogen level in the blood, and absence of hematuria and albuminuria. There is added one other symptom, viz., increased diuresis of a urine of low specific gravity. If we hold to the *modern theory* of kidney secretion as described by Cushny, we must ascribe this lack of concentration to the diminished ability to reabsorb water. There is no experimental proof that can be cited in support of this view, but Volhard and Fahr have shown in their Atlas that the cases of chronic diffuse glomerulo-nephritis show secondary changes in the convoluted tubules, resulting in changes in character and in flattening of the cuboidal cells. With such changes in the character of the cells a diminution of the function of absorption is at least possible. Dyes injected are completely excreted, but over a prolonged period of time so that a two hour specimen shows a diminution of the percentage excretion.

FUNCTION IN THE THIRD OR END STAGE OF DIFFUSE GLOMERULO-NEPHRITIS

The second or latent stage may last from a period of months to more than fifteen years. Ultimately it passes into the third or terminal stage with kidney insufficiency. The chronic inflammation gradually progresses with the formation of more and more connective tissue surrounding the glomeruli and the gradual

obliteration of the glomeruli in various degrees throughout the kidney. Filtration, despite the blood pressure above 250 mm. of mercury, maintained by a powerfully hypertrophied heart muscle becomes increasingly difficult. We may consider the beginning of the end stage when in spite of the hypertension, sufficient filtration is not possible and the rest nitrogen level persists above normal despite the reduction of the nitrogen intake to a minimum. This stage may last over months and even years but is always shorter than the second stage. As it progresses the nitrogen level gradually rises to a degree where symptoms of poisoning from the retained products of metabolism result. This is true uraemia. There is drowsiness, stupor gradually going into coma, tendon jerking, increased reflexes and the deep and slow breathing characteristic of states of acidosis. An unknown poison is being continually assumed by many investigators as the cause of the uremic symptoms, yet all the above symptoms can be sufficiently explained by the concentration in the blood of the non-protein nitrogenous substances, chief of which is urea, to over 200 mgm. per 100 cc. of blood, and of the ordinary acid products of metabolism, which, because of lack of filtration, are retained.

With the progress of the end stage, the ability to concentrate is further diminished and finally becomes fixed.

It is quite evident that when at any time during the progress of the second or third stage the mechanism of hypertension for any reason fails, filtration is at once markedly diminished and kidney function is the same as in the last of the end stage. In such cases of failure of the compensatory mechanism of hypertension, recovery does not occur as the rest nitrogen level quickly rises to extreme degrees.

Both the second and third stage may be complicated by an acute inflammation of the glomeruli. In such a case the symptoms of the acute stage of diffuse glomerular inflammation simply add themselves to the ones already present and we have in addition hematuria, albuminuria and cylindruria.

Diagnosis of the beginning of the end stage is often made easy by the appearance of a retinitis, most characteristically in the

form of a radiating star around the macula. This occurs only in the course of the end stage of diffuse glomerulo-nephritis, and on the border line between the second and end stages, so that when it appears, even with the normal rest nitrogen level in the blood, the course of the disease toward the terminal stage is definitely indicated.

KIDNEY FUNCTION IN BENIGN HYPERTENSION OR PURE SCLEROSIS OF THE KIDNEY VESSELS

Benign hypertension or pure kidney sclerosis or essential hypertension is characterized pathologically by changes in the smaller and smallest arterioles of the kidney, not affecting the afferent vessels of the glomeruli. The changes consist in thickening of the intima with a continual increase in and splitting of the elastic lamellae, thus narrowing the blood stream towards the glomeruli. Whenever arterioles are completely occluded, glomeruli and tubules disappear and are replaced by connective tissue. In the narrowed and thickened vessels, however, the resistance offered to the blood flow would lower the pressure in the glomeruli, were it not for the fact that the body is capable of raising the pressure in the arterial system, thus forcing more blood through the narrowed small vessels despite their increased resistance. The glomeruli and tubules are not diseased but are perfectly intact and functionally capable. This disease has long been known under various names. It is the arterio-capillary fibrosis of Gull and Sutton, the hyperpiesia of Albutt, the pre-sclerosis of Huchard, the latent sclerosis of von Basch, the primary granular kidney, etc.

Function in this kidney is entirely normal. Rest nitrogen level is normal, the urinary picture is normal except for a trace of albumin. Concentration ability is normal. Phenolsulphonephthalein is promptly excreted as in a normal kidney. Hypertension is of course dependent upon the extent of arterial changes and may range from only mild degrees such as 160 to 170 mm. of mercury to readings close to 300 mm. in extreme cases. Along with hypertension cardiac hypertrophy is of course present.

As long as the hypertrophied heart muscle is able to maintain itself against increased tension no symptoms appear. As soon as the heart fails to maintain itself, nycturia appears followed by edema of the extremities, paroxysmal attacks of dyspnea and, finally, with increased insufficiency of the heart muscle, all the symptoms and signs of heart failure. Nycturia often appears early when no other signs are present. This is not as in chronic diffuse glomerulo-nephritis the lack of concentration ability on the part of the kidney, but is due to a latent edema, really a pre-edematous stage, in which the retained fluid is eliminated by the kidney during rest at night. This can be proved by prescribing digitalis, a salt free diet with limited water intake, and rest in bed. The nycturia will then disappear or be reduced to a minimum. This is not the case with the nycturia of chronic diffuse nephritis. The same is true of the nightly attacks of cardiac asthma which are really due to a beginning pulmonary edema. The same treatment will cause these attacks to disappear.

Benign hypertension is often confounded with the second or chronic stage of diffuse glomerulo-nephritis in which hypertension is also the outstanding feature. Differentiation is practically always possible when we consider that in chronic nephritis the history of previous acute attacks can often be obtained, that concentration ability is diminished, and that increased water intake as well as dyes are excreted over a long period of time, while in benign hypertension concentration ability, water and dye excretion are normal.

The etiology of benign hypertension has been and still is the cause of a good deal of speculation. General arteriosclerosis has been assumed to be the etiological factor. This has been definitely disproved. Arteriosclerosis of the splanchnic vessels has been assumed by others. This too has been disproved. Nor is there any reason why arteriosclerosis of the mesenteric or splanchnic vessels should call for an increase in blood pressure. The result of arteriosclerosis everywhere is diminished blood supply to the organs and tissues affected, resulting in atrophy and other changes which we call "senile." These changes result in diminished activity of the organs affected quite in accordance with the diminished

blood supply brought to them by the sclerotic vessels. Although the total activity of the organs supplied by the splanchnic vessels is diminished, yet they are sufficiently able to fulfill the requirements of the body and nothing would be gained by an increase in blood pressure.

It is only in the kidney that this is necessary. Arteriosclerosis of the smaller and smallest arterioles in the kidney would diminish the amount of blood entering the afferent vessels of the glomeruli, and the pressure in the filter would be diminished, were it not for the increase in pressure forcing sufficient blood through the sclerotic vessels.

As to the cause of kidney sclerosis we are still in the dark. Plethora resulting from errors in diet may by continually increasing the blood supply to the kidney increase the wear and tear of the arterioles. Gout and lead are often factors. Excessive alcoholic intake can be discounted except in beer where probably the increased intake of fluid and increased nutrition are the main factors.

THE COMBINATION FORM OR MALIGNANT GENUINE CONTRACTED KIDNEY

In this form the arteriosclerosis of the finer and finest vessels extends to include the afferent vessels of the glomeruli. Added to this there is an acute nephritis. Hypertension is extreme. The kidney is entirely insufficient and the clinical picture resembles that of the end stage of diffuse glomerulo-nephritis.

CONCLUSION

I have so far followed the function of the kidney through the various forms of kidney disease known collectively as Bright's disease. It gives us a clear view of how the body attempts to correct any kidney affection sufficiently severe to affect kidney function. Such an understanding not only makes possible more accurate diagnosis, but also renders more exact the prognosis and treatment.



A PHARMACOLOGICAL STUDY OF OVARIAN AND CORPUS LUTEUM EXTRACTS, WITH A SPECIAL REFERENCE TO THE CONTRACTIONS OF THE GENITO-URINARY ORGANS

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INTRODUCTION

The importance of the endocrine glands in the physiological economy has in the past few years been more and more emphasized. While numerous papers on the subject have been published, our knowledge concerning their function and chemistry is still very deficient. The action of various glandular extracts on smooth muscle has been studied by a number of authors but their investigations were confined chiefly to the effects of such extracts on one or two organs and no systematic and quantitative study even of this phase of the subject, can be found with the possible exception of the paper by Itagaki (1).

The present authors have been engaged for some time in the study of the action of various glandular extracts on the movements of the genito-urinary organs. A detailed account of these investigations will appear in due time. In the present communication, it was found desirable to report the findings concerning the influence on the genito-urinary organs of only two glandular products; namely, ovarian and corpus luteum substances, because these substances were found to produce effects of exceptional interest from both scientific and practical points of view.

METHOD

Previous authors, such as Ott and Scott (2), Bell and Hick (3), Stickel (4), and Itagaki, have confined their studies to the effects of the above glands on the uterus. In the present investigation, the authors made a systematic study of both ovarian and corpus luteum extracts on all the principal genito-urinary organs. The organs studied were: The uterus and Fallopian tubes, the bladder and ureters and the vas deferens and seminal vesicles. The extracts employed were prepared both from fresh and from desiccated glands of various animals by extracting the same with cold physiological saline or Locke's or Tyrode's solutions. A few experiments were also made with alcoholic extracts of the glands which were evaporated and taken up in a saline solution. All the experiments were made on excised organs, suspended in the ordinary way in oxygenated Locke's or Tyrode's solutions. In studying such preparations, special attention was paid to the effect on the number and strength of contractions, the tonicity of the preparations, and also to the effects produced by varying the doses of the drugs studied.

ACTION ON THE BLADDER AND URETERS

Saline extracts of ovarian and corpus luteum substances were made by macerating or rubbing up the same with cold physiological saline or Locke's or Tyrode's solutions, allowing the suspensions to stand for an hour and filtering. The strength of the extract in all cases was made to correspond to 10 per cent of the fresh gland substance by weight. The effect of the extracts was studied on excised bladder preparations of the rat, pig, rabbit, and cat, and on the excised ureteral rings of pigs according to the method described elsewhere by one of the authors (5). It was found that neither ovarian nor corpus luteum extracts produced very much change in the contractions or the tonus of either the bladder or the ureters. It was only after very large doses of the drugs that a slight stimulation was noted. Thus, for instance, in the case of the rat, from 2 to 8 cc.

of corpus luteum extract (10 per cent) were required to produce such a change. In the case of the pigs', rabbits' and dogs' bladders, the doses required were, while not as great as those for the rat, also large. In case of the ureter, even larger doses of the extracts (3 to 10 cc. in 25 cc. of solution) produced practically no change in the contractions or tonus of the organ. The results of the various experiments are set forth in table 1. An analysis of all the data on the bladder and ureters points to the fact that neither ovarian nor corpus luteum extracts produce any

TABLE 1

Showing minimal stimulating doses of corpus luteum (L) and ovarian (O) extracts for the bladder and ureters on introducing the extracts into the chamber containing 25 cc. of Tyrode's solution

	NUM- BER OF EXPERI- MENTS	BLADDER	NUM- BER OF EXPERI- MENTS	URETER
Rat.....	18 {	L: 2.0-8.0 cc. O: 4.0-8.0 cc.	11 {	L: 3.0-10.0 cc. O: 3.0-10.0 cc.
Pig.....	9 {	L: 1.0 cc. O: 1.3 cc.		
Rabbit.....	6 {	L: (0.25)-0.5 cc. O: 0.5 cc.		
Cat.....	5 {	L: 0.25-0.5 cc. O: 0.5-0.7 cc.		

change in the contractions or the tonicity of those organs when administered in small doses, and that after very large doses of the extracts, there is a slight stimulation of the contractions and increase in the tonicity. As far as the authors have been able to ascertain, the only experiments on the bladder on record are those of Itagaki. This author performed three experiments with strips of the rabbit's bladder, and as a result of these experiments, he claimed that there was a diminution of tone after treatment with an extract of corpus luteum. The present authors have not been able to confirm his results (see figs. 1-3).

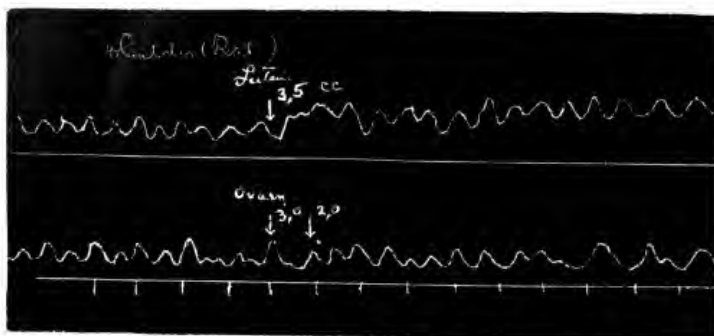


FIG. 1. SHOWING THE ACTION OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON RAT'S BLADDER.

The time markings in all the figures are in minutes. Note that 3.5 cc. of lutein extract (10 per cent) produces very little stimulation, and 5 cc. of ovarian extract (10 per cent) produce practically no change.

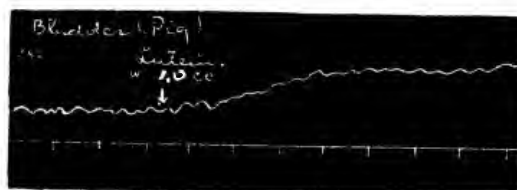


FIG. 2. SHOWING SLIGHT CONTRACTION OF PIG'S BLADDER ON ADDITION OF 1 CC. OF LUTEIN EXTRACT (10 PER CENT)

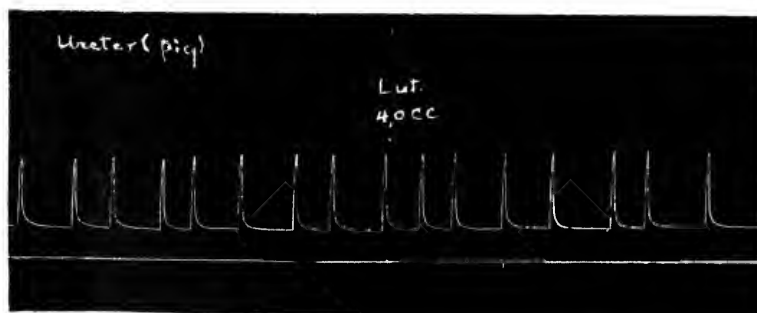


FIG. 3. SHOWING THE ACTION OF CORPUS LUTEUM EXTRACT ON PIG'S URETER 4 cc. of lutein extract (10 per cent in 25 cc.) produce no effect

ACTION ON THE UTERUS AND TUBES

A number of observers have studied the effect of ovarian and corpus luteum extracts on the uterus, but their findings do not agree with each other. Thus, for instance, Fuchs (6), working with the rabbit's uterus, reported a depressant action, Stickel found no effect on intravenous injection of ovarian extract, but a stimulating effect after corpus luteum, and Bell and Hick state that in the virgin rabbit's uterus no effect is produced, while the pregnant organ is stimulated by ovarian extracts. Ott and Scott found that both ovarian and corpus luteum extracts stimulated the excised uterus, and Itagaki, studying the effects of corpus luteum on the uterus of the rat, rabbit, cat, dog, and guinea-pig, found also a stimulation in the majority of his experiments. None of the previous observers attempted to determine the smallest effective dose of the extracts necessary to produce stimulation.

The present authors have made about 110 experiments with extracts of the ovary and corpus luteum on the excised uteri of the rat, guinea-pig, pig, dog, and cat, and also a number of experiments on the Fallopian tubes of the pig. It was found that in all cases both ovarian and corpus luteum extracts produced a powerful stimulation of the contractions and increase in the tonus of the uterus. It was also found that in all cases the excised uterus preparations reacted more quickly and to smaller doses of corpus luteum extracts than to extracts of the ovarian substance. Thus, for instance, in the case of the guinea-pig's uterus, 0.05 cc. or one drop of a corpus luteum extract in 25 cc. of Tyrode's solution was sufficient to elicit contractions, whereas the same preparation required 0.5 cc. of an ovarian extract to give a stimulating effect. The results of the experiments are set forth in table 2. It will be noted that in the case of the Fallopian tubes, corpus luteum extracts were also more effective than the extracts of ovarian substance (figs. 4-6). It may be well to emphasize in this place that while ovarian and especially corpus luteum extracts are quite stimulating to the uterus, this effect is not at all specific for these extracts, as a

stimulation of the uterus was found to be produced by extracts of nearly every gland or organ with which the authors experimented.

TABLE 2

Showing minimal stimulating doses of corpus luteum (L) and ovarian (O) extracts for the uterus and Fallopian tubes on introducing the extracts into the chamber containing 25 cc. of Tyroide's solution

	NUM- BER OF EXPERI- MENTS	UTERUS	NUM- BER OF EXPERI- MENTS	FALLOPIAN TUBE
Rat.....	24	{ L: 0.5 cc.* O: 0.5-1.0 cc.	{ 28	L: 0.15 O: 2.0-3.5 cc.
Guinea-pig.....	8	{ L: 0.05-0.15 cc. O: 0.5 cc.		
Pig.....	31	{ L: 0.05-0.25 cc.† O: 0.5-2.5 cc.		
Dog.....	12	{ L: 0.1-0.5 cc. O: 0.6		
Cat.....	41	{ L: 0.25-0.5 cc.† O: 0.5-3.0 cc.		

* In one case a slight decrease of tonus was seen.
† In one case no stimulation even after a dose of 25 cc.

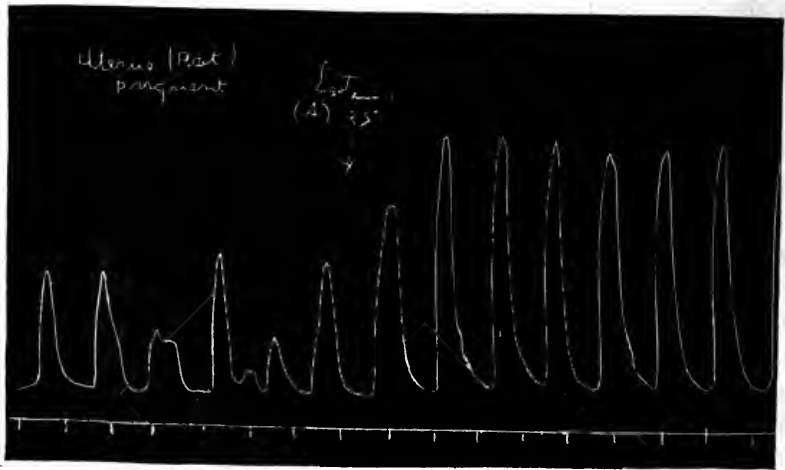


FIG. 4. UTERUS OF RAT, SHOWING EFFECT OF 0.5 CC. OF LUTIN EXTRACT

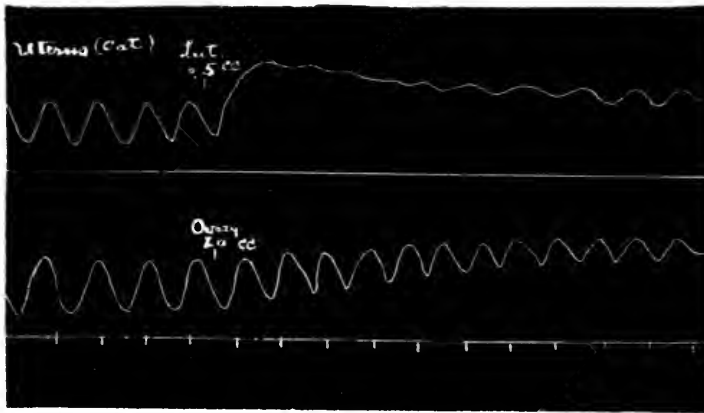


FIG. 5. SHOWING THE EFFECTS OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON THE MOVEMENTS OF CAT-UTERUS

Note difference in action between corpus luteum and ovary

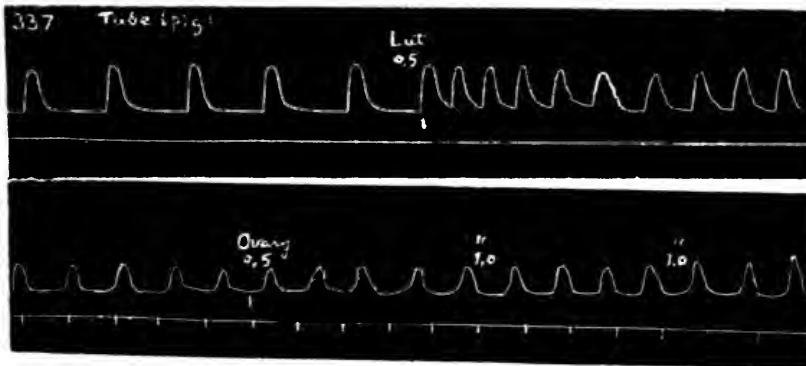


FIG. 6. SHOWING THE ACTION OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON FALLOPIAN TUBE OF PIG

Note the increased rapidity of rhythmic contractions as the result of administration of corpus luteum extract.

THE ACTION ON THE VAS DEFERENS AND SEMINAL VESICLES

While the comparative inactivity of ovarian and corpus luteum extracts for the bladder and ureters on the one hand, and their stimulating action on the uterus and tubes on the other hand may be of interest, these effects are not specific for those glands and can be produced by extracts of almost every other gland. The action of corpus luteum extracts on the vas deferens and the seminal vesicles, however, is of a very different and more specific character. No previous work on these organs in this connection is on record. The present authors have tested the action of all kinds of glandular extracts—ovarian, corpus luteum, suprarenal, thyroid, thymus, parotid, pituitary, prostate, placenta, mammary, testicular, liver, spleen and kidney—on the excised vasa deferentia of the rat, cat, guinea-pig, rabbit, and dog. A study of the results of the numerous experiments (over 300 in number) made evident a number of facts. In the first place, it was found that while all glandular extracts with the exception of epinephrin produce no changes in the contractions or tonicity of the vas deferens unless administered in very large quantities, that structure or organ exhibited extreme sensitiveness towards treatment with extracts of corpus luteum substance. In the second place, it was found that the quick response by contraction and increased tonus of the vas deferens toward corpus luteum extracts was, broadly speaking, proportional in degree to the quantity of the stimulating agent administered. In the third place, it was noted that while the vas deferens responded very quickly to the effects of even very small doses of corpus luteum extract, the same organ was not affected by ovarian extract except when very large doses of the same were used. Practically exactly the same observations were made in connection with the seminal vesicles of rats and guinea-pigs; only larger doses of corpus luteum were required to produce stimulation than in the case of the vas.

The most sensitive preparation for the testing of corpus luteum was found to be the freshly excised vas deferens of an adult rat. Such preparations, when suspended for an hour or longer in a

chamber containing 25 cc. of warm oxygenated Tyrode's solution, almost always responded with a slight contraction and increase in tonus to doses of 0.25 cc. of a corpus luteum extract, prepared by extracting a quantity of corpus luteum substances corresponding to 10 per cent of the fresh gland with cold saline or Locke's or Tyrode's solution for one hour and filtering. Occasionally the introduction of 0.05 cc. or about one drop of a 10 per cent solution of corpus luteum extract into a chamber containing 25 cc. of Tyrode's solution produced a response in the way of contraction of a vas deferens preparation. The only other glandular extract which stimulated contractions of the vas deferens in weaker concentrations than this is that of the suprarenal gland. It was found that epinephrin stimulated

TABLE 3

Showing minimal stimulating doses of corpus luteum (L) and ovarian (O) extracts for the vas deferens and seminal vesicle on introducing the extracts into the chamber containing 25 cc. of Tyrode's solution

	NUM- BER OF EXPERI- MENTS	VAS DEFERENS	NUM- BER OF EXPERI- MENTS	SEMINAL VESICLE
Rat.....	168 {	L: 0.05-0.25 (-0.5) cc. O: 1.0-3.0 cc.	96 {	L: 0.5-1.0 cc. O: 5.0-10.0 cc.

the vas deferens contractions in concentrations varying from four to six times less than the above.

A few details as to the performance of the test may be given in this place. Healthy adult rats are to be selected and the whole vas deferens should be excised under ether anesthesia. The vas is then suspended in a small chamber containing 25 cc. of Tyrode's or Locke's solution through which oxygen is bubbling, and the chamber is immersed in a water bath so as to keep the temperature constant. The vas is connected with the short arm of a light lever, and the long arm, which should be at least ten times as long as the shorter one, is arranged to record the contractions on a smoked kymograph. The normal vas of a rat exhibits practically no normal peristaltic movements or at most only very slight rhythmic contractions. On introduc-

tion of the drug or extract to be tested, a contraction of even a few millimeters is therefore to be regarded as a positive response. Before testing the potency of a new preparation, it is always advisable first to ascertain whether the vas deferens is active by treating it with a solution of lutein of known strength. If no response is obtained, the organ is to be discarded. If it is responsive, the preparation can then be washed with fresh Tyrode's or Locke's solution and the same organ used over again a number of times for testing other preparations. It is advisable to allow a vas deferens to remain in the test chamber for at least an hour before beginning to use it.

In studying the action of corpus luteum, the authors employed a number of well known commercial products of desiccated corpus luteum substance, and also suspensions or extracts of the fresh corpora lutea of a number of animals. All corpus luteum preparations exhibited a stimulating action on the vas deferens but the response was quantitatively different in case of different preparations employed. This fact led the authors to investigate the effects of various doses of any one preparation on a vas deferens and it was found that the degree of contraction varied, broadly speaking, with the dose of the drug administered. These findings may be illustrated by figures 7 to 14.

The results naturally suggest the use of the vas deferens for assaying corpus luteum. The authors have actually employed that organ for assaying various commercial preparations of corpus luteum and have found that they differed greatly in their potency. Whether the potency of a corpus luteum preparation as indicated by the vas deferens test is a true index of its physiological activity in therapeutics is not yet certain. It may be stated, however, in this place that the authors have gathered considerable clinical data from gynecologists, obstetricians, and other medical men, and that an examination of those data seems to reveal that the more potent preparations, as indicated by the vas deferens test, are also the ones which have given the most striking clinical results. For obvious reasons, it is impossible to publish more detailed data in that respect here. The authors have furthermore endeavored, as far as

possible to correlate the results given by the vas deferens tests of various preparations with other pharmacological effects produced by such preparations. As is well known, no very definite physiological or pharmacological properties exhibited by

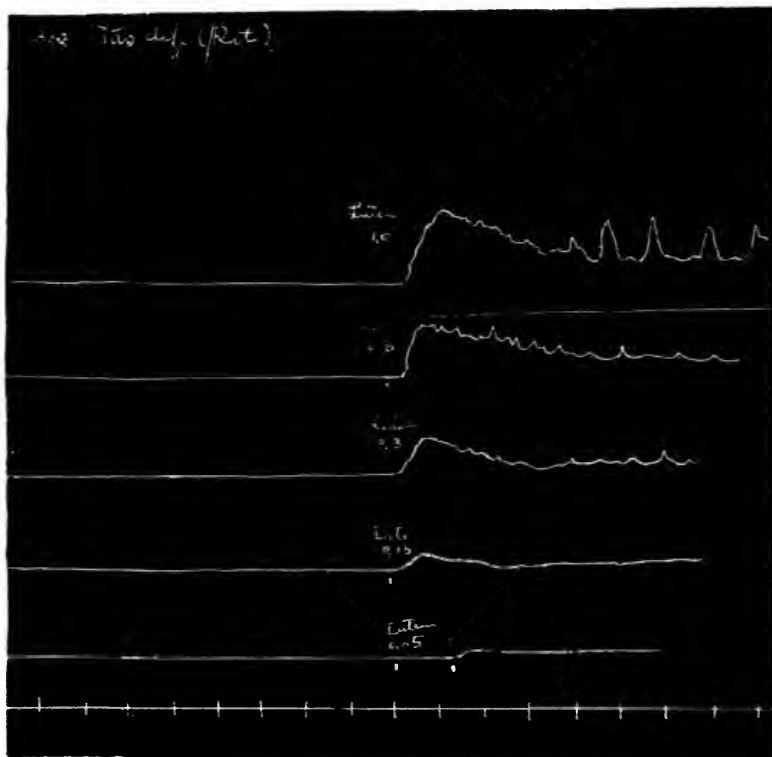


FIG. 7. VAS DEFERENS OF RAT

Series of curves showing effect of different doses (0.05 to 1.0 cc.) of corpus luteum extract. Same preparation was repeatedly used after thorough washing. The increase in tonus of the vas deferens is proportional in degree to the quantity of the extract administered.

corpus luteum have as yet been described. Halban (7) and others call attention to the stimulating effects of corpus luteum injections on milk secretion. Pearl (18) found that injections of corpus luteum in hens inhibit the laying of eggs. Boring



FIG. 8. SHOWING THE EFFECT OF A CORPUS LUTEUM EXTRACT ON VAS DEFERENS OF RAT

Note effect of three successive doses (0.5 cc., 0.5 cc., and 1.5 cc.)

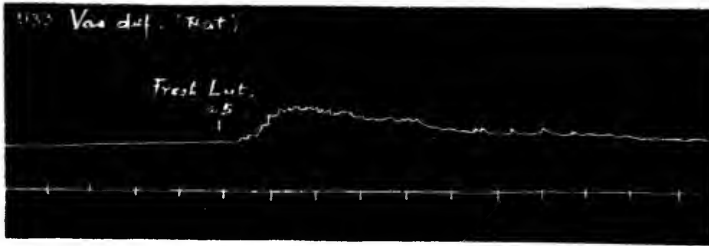


FIG. 9. SHOWING THE ACTION OF AN EXTRACT OF *Fresh* CORPUS LUTEUM OF PIG (0.5 cc.) ON VAS DEFERENS OF RAT



FIG. 10. SHOWING THE DIFFERENT RESPONSE OF THE VAS DEFERENS TOWARD THE ACTION OF OVARIAN AND CORPUS LUTEUM EXTRACTS

Note that 3 times 0.5 cc. of ovarian extract produce no effect, whereas, 0.4 cc. of corpus luteum produce marked contraction.

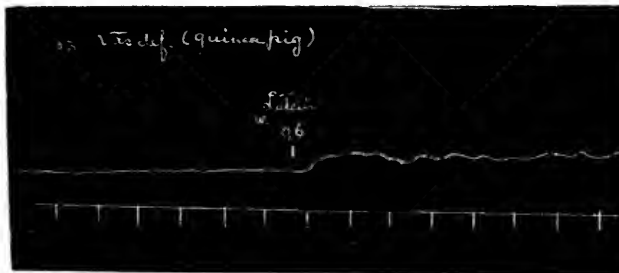


FIG. 11. SHOWING THE ACTION OF CORPUS LUTEUM EXTRACT (0.6 cc.) ON VAS DEFERENS OF GUINEA-PIG



FIG. 12. SHOWING THE ACTION OF CORPUS LUTEUM EXTRACT ON VAS DEFERENS OF CAT

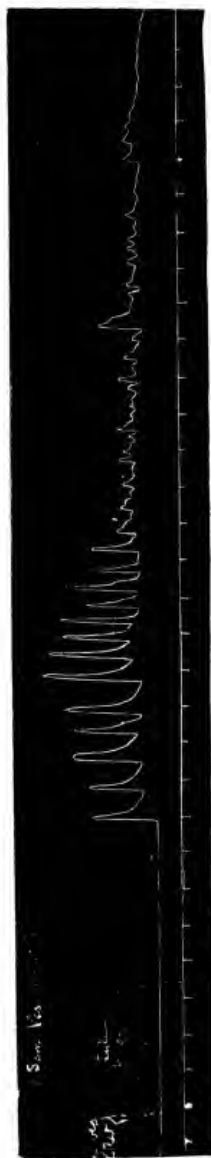


FIG. 13. SHOWING THE ACTION OF CORPUS LUTEUM ON SEMINAL VESICLE OF RAT
Quiescent seminal vesicle of rat stimulated to activity by 4 doses of 0.2 cc. each



FIG. 14. SHOWING THE MARKED DIFFERENCE IN ACTION OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON THE MOVEMENTS OF SEMINAL VESICLE OF RAT, 10 CC. OF THE LATTER PRODUCING NO EFFECT, WHILE 1 CC. OF THE FORMER ELICITS RHYTHMIC CONTRACTIONS

and Morgan (9) found that corpus luteum bears a certain relation to the feathering of fowl. All these observations, while extremely interesting are unsuitable for comparative study, not to say for standardizing of corpus luteum preparations. The present authors have studied to some extent two other effects produced by corpus luteum extracts which while perhaps of little significance, it is well to describe in this place. They are the changes in blood pressure and in the size of the frog's pupil.

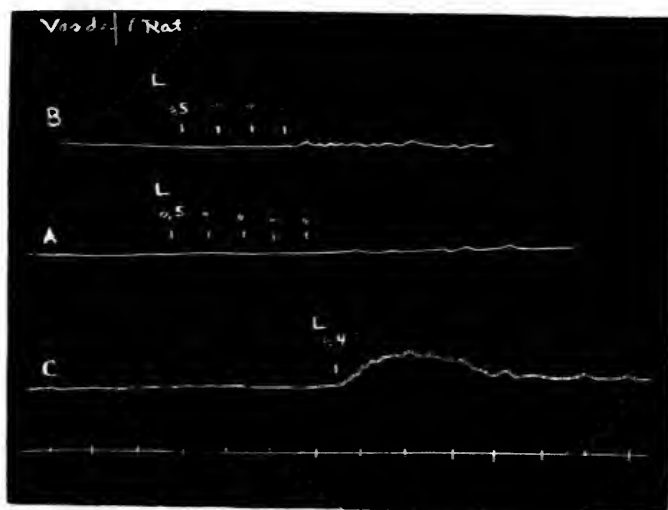


FIG. 15. SHOWING THE DIFFERENCE IN POTENCY OF THREE COMMERCIAL DESICCATED PREPARATIONS (A, B AND C) AS INDICATED BY THE VAS DEFERENS TEST

Preparation A begins to stimulate after 2.5 cc. of the aqueous extract. Preparation B begins to stimulate after 2.0 cc. of the aqueous extract. Preparation C begins to stimulate after 0.4 cc. of the aqueous extract.

As is well known, most glandular extracts, with the exception of those from the suprarenal and pituitary glands, produce a fall in blood pressure when injected intravenously. The present authors have studied the effect on the blood pressure of aqueous extracts of all kinds of glands and have found that extracts of corpora lutea, when injected intravenously in cats and dogs, also cause a fall in blood pressure. It was furthermore

noted that the degree of the fall varied with the potency of the corpus luteum preparations as indicated by vas deferens tests. Thus, for instance, a preparation which produced a marked

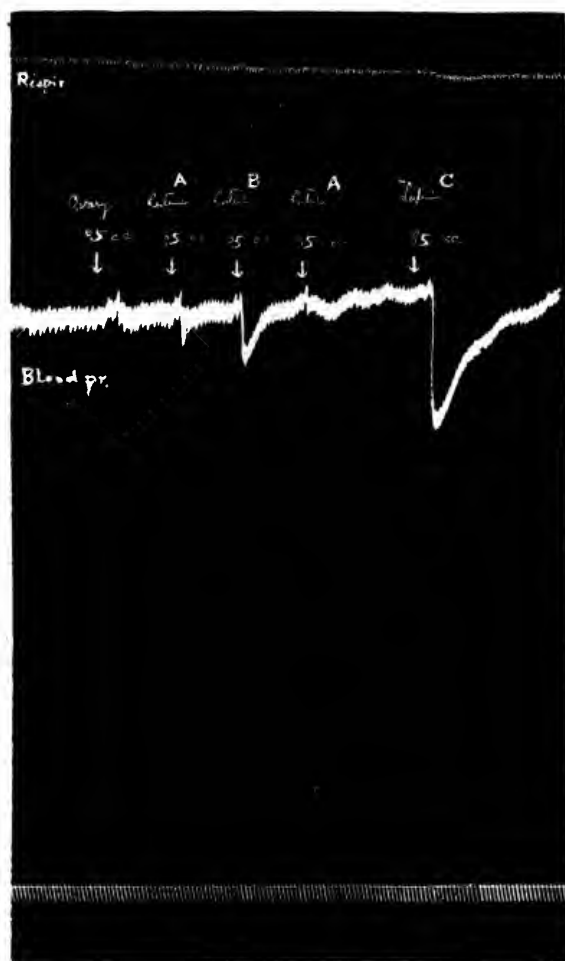


FIG. 16. EFFECT OF CORPUS LUTEUM AND OVARIAN EXTRACTS ON THE BLOOD PRESSURE OF CAT (WEIGHS 1.5 KG.M.)

A, B, and C are the three different commercial preparations used in figure 15. Time in 5 second intervals. Note that ovarian extract produces no fall in blood pressure, while the corpus luteum extracts produce a fall corresponding in degree to the vas deferens contraction.

stimulation of the contractions of the vas, also produced a marked fall in blood pressure on intravenous injection in a cat or dog. This is well illustrated by figures 15 and 16. It was interest-

TABLE 4*

Showing the effect of corpus luteum extracts on the pupil of frog's eye

CORPUS LUTEUM			TIME	CONTROL		
Strength, drug	Diameters of pupil			Strength, drug	Diameters of pupil	
	Before	After			Before	After
	mm.	mm.	min.		mm.	mm.
20% desiccated	2.7 x 1.5	3.4 x 2.2	30	20% ovary	2.7 x 1.7	3.0 x 1.9
20% desiccated	2.3 x 1.6	3.0 x 2.4	15	20% ovary	2.5 x 2.0	2.9 x 2.6
20% desiccated	2.6 x 1.9	3.0 x 2.3	140	20% ovary	2.8 x 2.3	2.7 x 1.8
10% desiccated	2.8 x 1.6	3.5 x 2.3	25	10% ovary	2.8 x 1.8	3.1 x 2.0
10% desiccated	2.3 x 1.8	3.3 x 2.9	45	10% ovary	2.6 x 2.0	3.0 x 2.8
10% desiccated	2.3 x 1.7	3.0 x 2.6	10	10% ovary	2.6 x 2.1	2.8 x 2.2
10% desiccated	1.9 x 1.5	2.5 x 1.7	40	10% ovary	2.1 x 1.5	2.3 x 1.5
10% desiccated	1.8 x 0.9	2.5 x 1.5	60	Locke's solution	1.7 x 0.8	1.7 x 0.9
10% desiccated	2.1 x 1.5	2.5 x 2.0	60	Locke's solution	2.5 x 1.7	2.0 x 1.7
10% desiccated	2.3 x 1.7	2.6 x 1.9	30	Locke's solution	2.1 x 1.5	2.2 x 1.6
5% desiccated	2.9 x 2.1	3.0 x 2.3	40	5% ovary	2.9 x 2.0	2.9 x 2.0
5% desiccated	2.5 x 1.8	3.0 x 2.0	30	5% ovary	3.0 x 1.5	3.0 x 1.8
5% desiccated	2.8 x 1.6	3.0 x 2.3	20	5% ovary	2.7 x 1.6	2.5 x 1.3
5% desiccated	2.5 x 1.5	2.7 x 1.8	80	5% ovary	2.7 x 1.7	2.7 x 1.8
5% desiccated	2.1 x 1.3	2.8 x 2.0	45	5% ovary	2.3 x 1.3	2.5 x 1.6
20% fresh	2.1 x 1.6	2.8 x 2.5	25	20% ovary	2.1 x 1.8	2.7 x 1.9
10% fresh	2.6 x 1.7	3.0 x 2.5	20	10% ovary	2.6 x 1.7	2.7 x 1.8
10% fresh	2.7 x 2.0	3.2 x 2.6	25	10% ovary	2.7 x 2.0	2.8 x 2.0
10% fresh	2.5 x 2.1	2.5 x 2.0	40	10% ovary	2.5 x 2.3	1.6 x 1.2
10% fresh	2.6 x 1.9	2.8 x 2.1	110	10% ovary	2.8 x 2.3	2.7 x 1.8
10% fresh	2.3 x 1.8	2.7 x 2.1	20	Locke's solution	2.2 x 1.5	2.3 x 1.7
10% fresh	2.3 x 1.7	2.6 x 1.9	35	Locke's solution	2.1 x 1.5	2.2 x 1.6
10% fresh	2.5 x 1.7	3.0 x 2.5	20	Locke's solution	2.6 x 1.7	2.7 x 1.8
10% fresh	2.5 x 2.1	3.0 x 2.8	10	10% placenta	2.5 x 2.3	2.5 x 2.3
10% fresh	2.5 x 2.0	2.5 x 2.0	35	10% placenta	2.5 x 2.2	2.0 x 1.5

* The experiments described in this table were made with desiccated and fresh corpus luteum of the sow free from preservatives, furnished by the courtesy of Hynson, Westcott & Dunning Company, and with desiccated ovarian substance of the sow furnished by the courtesy of the Armour Company.

ing to note that while corpus luteum extracts tend to produce a fall in blood pressure, extracts of ovarian substance proper of the same concentration in terms of fresh gland did not affect the blood pressure, nor did they stimulate the vas deferens.

The authors, in connection with their experiments with corpus luteum preparations, have made systematic observations on the effect of such preparations on the pupil of the frog's eye. As a result of numerous experiments with proper controls it may be stated that aqueous extracts of potent corpus luteum preparations (the potency being expressed in terms of the vas deferens test) produce a distinct dilatation of the frog's pupil, the degree of dilatation and the time of its onset depending upon the concentration of the solution. Here again it is remarkable to find that ovarian extracts do not produce any dilatation of the pupil, thus distinguishing them from the corpus luteum preparations (see table 4). Further details concerning the action on the pupil are published elsewhere (10).

DISCUSSION

An analysis of all the experiments described above reveals several interesting facts. In the first place it is evident that the action of corpus luteum extracts on the smooth muscle of different excised organs is, contrary to what might have been expected, not identical. Thus, it was found that the effect on the bladder and the ureters is very slight, while that on the uterus and tubes is very marked. The stimulating action of both ovarian and corpus luteum extracts on the excised uterus, however, is not at all surprising, for it has been found by the present authors as well as a great many other observers that uterine muscle is stimulated by treatment with extracts of almost every organ or gland. In fact in the experience of the present authors, the uterus and the intestine are the least reliable organs for the study of the effects of pharmacological agents on smooth muscle, because both of these organs are extremely liable to variations due to changes in temperature, to slight changes in oxygenation, to changes in the surrounding media and to changes due to the species of animal from which the organs are obtained and the time of its death. The marked stimulation of the uterus and the intestine *in vitro*, observed by the present investigators, is therefore not in any sense specific or unusual.

In the second place it has been shown that the vas deferens and seminal vesicles, especially the former, exhibit an extraordinary sensitiveness to the effects of corpus luteum extracts, reacting by contraction to treatment with such extracts in doses entirely inadequate for stimulation of other forms of smooth muscle on the one hand, and not reacting to very much larger doses of extracts of other glands on the other hand. In this sense the vas deferens reaction for corpus luteum can be spoken of as being more specific than, for instance, the reaction of the uterus for pituitary extracts, for, as is well known, even minute doses of pituitary extract will stimulate intestinal muscle almost as powerfully as they will produce contractions of the uterus.

In the third place, it has been definitely established that extracts of corpus luteum and extracts of ovarian substance proper do not act on excised muscle in the same identical way. The vas deferens reaction is characteristic for the corpus luteum only and not for the ovarian residue.

The explanation of the peculiar behavior of the vas deferens on treatment with corpus luteum is not at hand. It is interesting, however, to state in this place an additional fact; namely, that the only other glandular extract (always excepting epinephrin) which comes nearest to corpus luteum in its stimulating influence on the vas deferens is that obtained from another sexual gland, the testis. It was found that testicular extracts were also very stimulating to the vas deferens. The dose of testicular extract required to produce contraction for any one vas deferens preparation is, however, about double that of corpus luteum extract for the same preparation (fig. 17).

In the fourth place, it has been shown that the degree of contraction of the vas deferens is, physiologically speaking, proportional to the dose of the extract administered. This fact suggests the use of such a preparation in assaying corpus luteum. Whether such a test is a fair criterion as to the physiological potency of various preparations in clinical practice cannot of course be at present definitely determined. It was shown, however, that the potency of the corpus luteum extract, as indicated by the vas deferens reaction, ran parallel to the effects

of the blood pressure and on the frog's pupil, and as far as could be gathered, agreed with the clinical experience of a number of physicians.

The vas deferens test for corpus luteum may be considered useful, not only for the assaying of different corpus luteum preparations, but may also serve a good purpose in the search for the active principle or principles of the corpus luteum. Thus, for instance, a chemist who obtains a number of chemical derivatives of the gland may quickly determine which fraction contains a body resembling in its properties the corpus luteum. The present authors may cite two illustrations to the point. In one

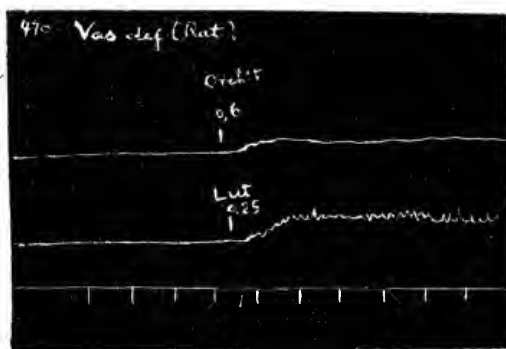


FIG. 17. SHOWING THE ACTION OF TESTICULAR EXTRACT ON VAS DEFERENS OF RAT, AS COMPARED WITH EFFECT OF CORPUS LUTEUM EXTRACT ON SAME PREPARATION

case a quantity of fine white crystals was sent to them by a chemist who stated that the crystals were obtained from corpus luteum substance, and that he thought they were physiologically active and represented the active principle of that gland. The vas deferens test was negative even after large doses of the drug, and therefore did not speak in favor of the crystals being the active principle. Later chemical investigation revealed that the crystals consisted of a mixture of chloresterin and fatty acids. The other illustration is of a different character. Frank and Rosenbloom (11), working with extracts of the placenta, obtained some chemical preparations which suggested to them a

relationship between the placenta and corpus luteum. Indeed, it was claimed by the authors that certain physiological effects, such as hypertrophy of the uterus and increased secretion of milk were produced by injections of extracts of either the placenta or corpus luteum. The present authors have worked with extracts of the desiccated placenta of the sow, and of the fresh placenta of the cat. As far as the vas deferens test is concerned, extracts of dry placenta substance gave no reaction at all, while extracts of fresh placenta produced contraction of the vas only after very large doses, and such contractions could be produced by similar large doses of all kinds of glands. The vas deferens test, therefore, does not speak in favor of placental and corpus luteum extracts as being identical. At least we are warranted in assuming that this reaction is certainly due to a constituent of corpus luteum either not found in the placenta at all or present in it only in infinitesimal quantities.

It was stated above that the corpus luteum extracts produced a marked fall in blood pressure after intravenous injections in cats and dogs. Inasmuch as the fall in blood pressure is produced by such injections of extracts of all kinds of glands and tissues, and inasmuch as there is some evidence that such a fall in blood pressure may be due to the presence in the various tissues of a body in the nature of histamin or beta-imido-azoly-ethyl-amine, it was interesting to inquire whether the vas deferens reaction is given by histamin. Accordingly some experiments were made to that effect. It was found that small doses of histamin produced a very profound fall in the blood pressure of a cat, but that the same quantities and even larger quantities of the drug failed to stimulate the contraction of the vas deferens. Experiments with histamin on the frog's eye failed also to show a dilatation of the pupil after that drug. The vas deferens reaction to corpus luteum extracts cannot therefore be said to have any special relation to the presence of a histamin-like body in that gland.

SUMMARY

1. The action of fresh and desiccated ovarian and corpus luteum extracts was studied on the following genito-urinary organs: bladder and ureters, uterus and Fallopian tubes, vas deferens and seminal vesicles of various animals.

2. Corpus luteum extracts have very little effect on the contractions and tonicity of the excised bladder or ureters.

3. Corpus luteum extracts exert a very stimulating effect on the excised uterus and Fallopian tubes, but their action on these organs is not specific as the same effects are produced by administration of extracts of all kinds of glands.

4. Corpus luteum extracts exhibit a markedly stimulating action on the excised vas deferens and seminal vesicles, and this reaction may be spoken of as specific inasmuch as the vas deferens and seminal vesicles are stimulated by doses of corpus luteum extracts which are entirely inadequate for stimulation of other forms of smooth muscle on the one hand and the same organs are not stimulated by very much larger doses of extracts of other glands on the other hand.

5. In respect to their effect on all the genito-urinary organs studied, ovarian extracts exert a very much weaker action than corpus luteum extracts.

6. The peculiar and sensitive reaction of the vas deferens of the rat to the effects of corpus luteum extracts is, physiologically speaking, proportional in intensity to the doses of the drug used, and runs parallel to the effects of the same extracts on the blood pressure and on the pupil of the frog's eye. It, therefore, offers a convenient method for the assaying of corpus luteum preparations on the one hand, and for the testing of the physiological activity of various chemical derivatives of the corpus luteum on the other.

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WAR NEPHRITIS¹

A CLINICAL, FUNCTIONAL, AND PATHOLOGICAL STUDY

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Owing to the comparative rarity of acute nephritis in civil practice few opportunities have been afforded for a study of renal function from the earliest stages of the disease. The occurrence of a large number of cases of this condition among our troops on active service presented, therefore, a unique occasion for its clinical, functional and pathological study.

This investigation was carried out at a base hospital equipped with adequate laboratory facilities for this type of work. We had the additional advantage of being in charge of a ward specially reserved for cases of nephritis. Thus our laboratory work was never divorced from clinical observation. The data presented in this paper have been obtained from thirty-three cases specially selected from some three hundred which have passed through our hands. These were all typical cases of war nephritis, and, with one exception, only those were included which from their previous history and clinical condition negatived as far as possible a previous nephritic condition.

PLAN OF INVESTIGATION

As long as the patient showed any edema or other serious symptom he was kept on a regulated fluid diet of 2200 cc., of which 1800 cc. were milk. This diet contained from 2.5 to 3 grams of chlorides as shown by analysis and about 12 grams of nitrogen as estimated from tables. As the edema cleared up and the general condition improved, bread and butter and milk puddings were added. Later on, chicken or fish, vegetables,

¹ A report to the Medical Research Committee.

and fruit were permitted. It was naturally impossible in a military hospital to keep this increased diet strictly uniform, but on an average it contained about 4 grams of chlorides and about 15 grams of nitrogen.

The daily output of urine was measured, its specific gravity taken, the total excretion of albumin calculated by Esbach's albuminometer, and the presence or absence of blood noted. At frequent intervals fresh specimens of urine were centrifugalized and the sediment examined in regard to its pathological contents.

Much time was devoted to the estimation, both in the blood and in the urine, of certain substances normally excreted by the kidney. Chief attention in this respect was given to urea and chlorides. In the blood we estimated the amount of urea and the total non-protein nitrogen and the chloride concentration of the plasma. The urea in the blood was estimated by Folin's modification of Marshall's urease method (1), the total non-protein nitrogen by Folin's micro-Kjeldahl method (2), and the plasma chlorides by the McLean-Van Slyke method (3).

The urinary chlorides were estimated daily by Volhard's method. Towards the end of the patient's stay in hospital, and when the output of chlorides in his urine was regular, the patient was given a single additional 10 grams of sodium chloride. The elimination of this extra salt and its effect on the chloride concentration of the urine and on the total quantity of urine passed was noted.

In certain cases daily estimations of the amount of urea excreted were made by Marshall's method (4). In addition, the urea in the urine was estimated at the same time as the urea in the blood, to obtain the necessary data for Ambard's coefficient (5) of urea excretion. The formula employed was:

$$\frac{\text{Ur}}{\sqrt{D \times \sqrt{\frac{C}{5}}}} = K.$$

Ur = grams of urea per litre of blood.

D = grams of urea excreted in twenty-four hours; calculated from excretion in one hour.

C = grams of urea per litre of urine.

The excretory power of the kidney in eliminating a substance foreign to the organism was also studied. For this purpose we employed phenolsulphonephthalein, following the original technique of Rowntree and Geraghty (6) except that the injection was given intravenously instead of intramuscularly, so that the edema often present in these cases should not interfere with the absorption of the dye.

In addition to the above purely functional tests of renal efficiency, repeated examinations were made as to the acid base relationship in the blood. The subject was studied by three methods:

1. By the estimation of the alveolar carbon dioxide tension in the alveolar air by the method recently devised by Marriott (7).
2. By the estimation of the alkali reserve of the blood by the Rowntree-Marriott (8 and 9) collodion sac method.
3. By the estimation of the combined carbon dioxide of the plasma by Van Slyke's (10) pipette.²

CLASSIFICATION OF CASES

As the investigation proceeded it became evident that, although the majority of the cases rapidly improved, yet a considerable proportion recovered very slowly from their initial symptoms and steadily tended towards chronicity. Hence two main groups, resolving and non-resolving, could be distinguished. Certain cases, however, lay on the border-line and tended to merge these two types into one another, thus preventing an absolute line of demarcation between the two.

Separate sections are devoted to the fatal cases and to those in which a relapse was the outstanding clinical feature. In

² Normal functional values: A continued daily urinary output of 2000 cc. or over has been considered to constitute a diuresis. In the blood 45 mgm. per 100 cc. of urea and total non-protein nitrogen were fixed as the upper limits of normal. Normal figures for plasma chlorides, 560-620 mgm. per 100 cc.; Ambard's coefficient of urea excretion, 0.06 to 0.09; phthalein excretion, 60 to 75 per cent in one hour; alveolar CO₂ tension, 38 to 45 mm. Hg; R_pH, 8.3 to 8.5; and combined CO₂ in plasma, 55 to 78 cc.

another section, in addition and not included in our series, are discussed cases of acute nephritis following a definite focal infection which, differing in many respects from typical war nephritis, we have termed infective. This latter is the same form of acute nephritis which is often seen in civil life as a sequel to acute infections.

RESOLVING GROUP

Twelve cases which presented similar clinical symptoms and functional disturbances were selected for special study (table 1). They arrived at the base five to thirteen days after onset and remained in the hospital for about one month. All had definite edema of the face and lower back, while some in addition had swelling of the lower legs and signs of fluid in the chest cavity. On admission, dyspnea was present in eight cases, being most marked in three which also had signs of bronchitis. Four, though still edematous, were quite free from respiratory distress. The edema cleared up rapidly, disappearing within ten to twenty-five days from onset. With the disappearance of edema there was always a definite increase in the excretion of urine. In ten cases this pouring out of substances retained in the body was marked by a diuresis lasting for several days, while in two cases an increased elimination was indicated by a moderate polyuria persisting during the entire edematous period. General clinical improvement was very noticeable with the onset of increased urine excretion. In ten cases systolic blood-pressure determinations, which before diuresis had ranged from 140 to 170 mm. Hg, showed a distinct fall after diuresis to 100 to 125 mm. Hg. In the remaining two the blood-pressure was within normal limits throughout. On ophthalmoscopic examination slight neuroretinal edema about the margin of the optic disk was found in four out of twelve cases, but lesions of a more severe type, such as hemorrhages and areas of degeneration, were never observed. The temperature rose to 99° or 100° in several cases without any determinable cause.

Routine urine examination. The specific gravity tended to be low during diuresis. However, following the output of re-

tained fluid the urine concentration soon rose. This occurred in nine cases within four to five weeks from onset. In only three cases did it continue to remain as low as 1.010 to 1.013 from five to seven weeks after the beginning of the disease. The amount of albumin in the urine decreased as a rule with improvement in renal excretion. In one case the original amount, 0.1 per cent, persisted during the patient's entire stay in the ward. Generally the number of casts also diminished along with the decrease of albumin, but in three cases casts were just as numerous at the time of discharge as on admission. While macroscopic blood was observed in the urine of only three cases, red blood corpuscles were present microscopically in all cases. Polymorphonuclear leucocytes and large round mononuclear cells, often containing blood-pigment, were of frequent occurrence.

Functional studies. Renal functional tests were commenced within two weeks of initial symptoms and repeated several times during the stay in hospital. From the time of admission phenolsulphonaphthalein was well excreted, the output varying from 40 to 66 per cent. One case admitted in convulsion excreted as low as 25 per cent, but a week later the figure stood at 60 per cent. The urea content of the blood was slightly raised in four cases, being 46 to 57 mgm. per 100 cc., but after diuresis it fell to normal. Accompanying this fall in blood-urea the total output of urea in the urine rose. In four other cases there was a corresponding decrease in the total non-protein nitrogen of the blood from 47 to 62 mgm. per 100 cc. to 27 to 39 mgm. The amount of urea in the blood was quite normal in the remaining four cases during their entire stay in the hospital, and the total non-protein nitrogen determined in three of these was also normal. Estimation of the chlorides in the plasma showed a high initial amount in six cases, but following diuresis there was a gradual fall to normal. In three of the six cases during flood diuresis there was an early fall in the plasma chlorides with a moderate second rise when the amount of urine diminished. When edema was present three cases had a normal plasma chloride content. During diuresis there was always a marked increase of the total chlo-

TABLE 1
Resolving group

PATIENT, AGE, DATE OF ADMISSION	DAY OF DISEASE	TEMPERATURE	EDEMA	BLOOD PRESSURE		URINE				PHENOLSULPHONEPHTHA- LEIN per cent	BLOOD				AMBRAND'S COEFFICIENT	ACID-BASE RELATIONSHIP			REMARKS
				mm. Hg.	per cent	Amount cc.	Specific gravity	Albumen per cent	Gross blood		Chloride per cent	Chloride mgm. per 100 cc. plasma	Urea mgm. per 100 cc.	T. N. P. N., mgm., per 100 cc.		Alveolar CO ₂ ten- sion mm. Hg.	RpH	Combined CO ₂ of plasma volume	
J. S., 28, 10 /iv /17..	6	99	++	150	1320	1.020	0.4		0.18	65									
	16	N	0	105	4300	1.008	0.02		0.30	613									
	41	N	0	105	2420	1.014	0.17		0.27	69									
A. B., 31, 14 /iv /17.	10	N	++	120	1065	1.014	0.25		0.17	55									
	14	N	++	110	1635	1.010	0.08		0.24	597									
	31	N	0	1560	1.008	0.05			0.21	62	648	39			33	8.1			
	41	N	0	115	1195	1.016	0.07		0.39	60	631				37	8.2			
K. A., 20, 23 /iv /17.	5	99	++	160	2425	1.010	0.10		0.39	62	658	47			25	7.9			
	12	N	0	100	1635	1.012	0.05		0.30	570	43				38				
	28	N	0	100	1575	1.017	0.05		0.32	75	606	29							
L. E., 36, 9 /v /17...	10	N	++	145	1965	1.010	0.18		0.30	60	666	53			33	8.0			Previous attack of war nephritis, June, 1915; in hospital till Novem- ber, 1915; returned to France, January, 1917
	26	N	0	120	2145	1.010	0.04		0.38		580	33							
	37	N	0	120	1820	1.010	0.05		0.27	66	553	31	27		39				

[illegible]

rides in the urine, while in half the cases the chloride concentration was increased, resulting in what French workers term a chloride "debâcle." The disappearance of the edema corresponded closely with the termination of high chloride excretion. The addition of 10 grams of salt to the diet just before evacuation from the hospital gave the following results: four cases which had showed increased concentration of chlorides in the urine during diuresis excreted the extra salt by a rise in chloride concentration; five cases with an original normal concentration eliminated the extra salt either by diuresis or by an increase in concentration; the remaining three failed to excrete the extra salt satisfactorily, although during diuresis the concentration had been good; the onset of hematuria some time after the original diuresis was thought to bear some relationship to this later failure in chloride excretion.

Acid-base relationship. Early in the disease nine of the twelve cases had a definitely diminished alveolar CO_2 tension, ranging between 25 and 35 mm. Hg. In order to confirm this evidence of a mild degree of acidosis, the alkali reserve of the blood was determined by Marriott's method in three of these cases. The moderately reduced R_pH of 7.9, 8.0, and 8.2 corresponded to the alveolar CO_2 tensions of 25, 33, and 35 mm. Hg. Simultaneous estimations of the combined CO_2 of the plasma and alveolar CO_2 tensions were also made in three others. Here again the alveolar CO_2 tensions of 32, 33, and 35 mm. Hg were associated with a condition of diminished alkali reserve in the blood—the combined CO_2 amounting to 40, 46, and 48 cc. Following diuresis and general improvement, the three determinations indicated a rapid rise to the normal (see table 1). With one exception this restoration took place without the use of alkali therapy. On the other hand, one case, E. I., had no evidence of an acidosis previous to the onset of a marked diuresis nor during the subsequent course of the illness.

NON-RESOLVING GROUP

In a certain number of cases the delayed onset in general improvement and slow disappearance of edema indicated a more severe type of renal disease than in the resolving type previously described. Ten cases of the present series belong to such a group (table 2). On admission, one to three weeks after reporting sick, all showed moderate or marked general edema, complained of general weakness and lack of appetite, and in eight of the ten cases dyspnea was present. On the routine diet and hot packs improvement was slow, and the diuresis which ensued so quickly under similar conditions in the resolving cases was delayed. Even when the increased urinary elimination did commence, as indicated by a distinct diuresis or intermittent polyuria, the edema disappeared slowly and several cases had not entirely resolved until a second diuresis had occurred. In the most protracted case of this type, W. V., oedema was still present at the end of three months. With this exception the last trace of edema disappeared in two to seven weeks after onset as compared with one to three weeks in the resolving type. During recovery these patients were very susceptible to mild relapses, the occurrence and details of which are discussed below, and a secondary anemia always developed while in the hospital. Three cases on admission had a systolic blood pressure varying between 165 and 170 mm. Hg, which before evacuation had fallen to 120 mm. Hg. In four cases the blood-pressure varied between 90 and 140 mm. Hg. during their stay in hospital. In three cases with long-persisting edema the blood-pressure was quite normal throughout in two, while in a third, W. V., it continued to be high—160 to 200 mm. Hg up to the time of evacuation. Changes in the eye-grounds were fairly common, abnormalities being observed in six of the cases. Two had neuro-retinal edema only, two a few isolated hemorrhages, while two others developed both areas of degeneration and hemorrhages as the disease progressed. The development of these changes was of interest in W. V., the case with persistent edema and high blood-pres-

TABLE 2
Non-resolving group

PATIENT, AGE, DATE OF ADMISSION	DAY OF DISEASE	TEMPERATURE degrees	EDEMA	BLOOD PRESSURE mm. Hg.	URINE					PHENOLSULPHONEPHTHA- LEIN	BLOOD				AMBAHD'S COEFFICIENT	ACID-BASE RELATIONSHIP			REMARKS
					Amount cc.	Specific Gravity	Albumen per cent	Gross blood Chloride per cent	Chloride per cent		Chloride mgm. per 100 cc. plasma	Urea mgm. per 100 cc.	T. N. P. N. mgm. per 100 cc.	Alveolar CO ₂ ten- sion		RpH	Combined CO ₂ of plasma volume		
W. C., 38, 7/iv/17..	10	N	++	106	850	1.010	0.50		0.06	20	613			65					Sodium bicarbonate, 16 grams per diem, 41st- 63d day of disease Sodium bicarbonate, 16 grams discontinued, 63d- 76th day of disease Sodium bicarbonate, 16 grams readministered, 77th-82d day of disease
	31	N	+	95	2340	1.010	0.38	+		29	672			56		23	7.8		
	55	99	Tr.	140	2735	1.010	0.25		0.20	29	590			37		39	8.2		
A. S., 39, 11/iv/17..	76	N	0	110	2160	0.010	0.15	+	0.20	21	640	132	73	0.333		30		37	Sodium lactate, 16 grams per diem, 39th-57th day of disease
	82	N	0	110	2450	1.009	0.10	+	0.29	18	656	158				35		54	
	14	N	++	120	1605	1.010	0.70		0.05	38	645			87		25			
A. S., 39, 11/iv/17..	36	99	+		1800	1.010	1.00		0.27	60	650			30		25	8.1		Sodium lactate, 16 grams per diem, 39th-57th day of disease
	57	N	0	115	2140	1.014	0.70		0.43	64	600	41	37			35			

TABLE 2—Continued

PATIENT, AGE, DATE OF ADMISSION	DAY OF DISEASE	TEMPERATURE	EDEMA	BLOOD PRESSURE				URINE				PHENOLSTICPHONEPHTHA- LEIN				BLOOD				AMBAUD'S COEFFICIENT	ACID-BASE RE- LATIONSHIP		REMARKS
				mm. Hg.	cc.	Amount	Specific gravity	Albumen	Gross blood	Chloride	per cent	per cent	Chloride mgm. per 100 cc.	Urea mgm. per 100 cc.	T. N. P. N. mgm. per 100 cc.	Alveolar CO ₂ tension	Rph	Combined CO ₂ of plasma volume					
W. V., 48, 7/viii/17	13	N	++	165	606	1.009	0.70	0.09	17	624	137	552	140	94				42	8.4	55	Sodium bicarbonate, 13th- 93d day of disease		
	29	N	+++	165	865	1.011	1.20	+	0.06			511	113	84				42					
	28	99	+++	160	1015	1.013	1.60	+	0.03	10	490	102	68				42						
	37	N	+++	1170	1.010	1.00	+	0.02			31	600	51	46				42					
	71	N	++	170	1780	1.008	0.70	0.21	31	600	51	46						42					
	93	99	+	170	2382	1.013	0.55	+	0.38	22	601	52	40	0.161				43		67			
W. G., 46, 23 /viii/17	9	N	+++	140	495	1.012	0.40	0.13	32	658	140	103						28	7.9	37	Sodium bicarbonate, 14th- 67th day of disease		
	21	99	+++	120	1320	1.018	0.10	0.12	50	594	71							39		59			
	50	N	0	135	2570	1.006	0.10	0.33	42	622	31			0.101				43		59			
	67	N	0	115	2300	1.014	0.08	0.42	62	587	35	30	0.098				45						
H. W., 39, 12/x/17..	18	N	+++	170	680	1.027	0.40	0.30	48		90	74						32		43	Convulsion on admission		
	25	N	++	140	1990	1.008	0.40	0.33	59		32	27	0.100					40		54			
	44	N	+	130	2100	1.011	0.20	+	50		43	37	0.134					40		54			
	58	N	0	110	2210	1.008	0.12	0.39	46		54	42	0.156					40		50			
	65	N	0	1460	1.014	0.18	0.40		40		60	48	0.165					38		47			

sure previously mentioned. On the seventeenth day of the disease the eye-grounds were normal. The next examination was made on the fiftieth day, when neuroretinal edema, numerous hemorrhages, and one small pale area suggesting early degeneration were present. Later, on the ninetieth day, the eye-ground picture was quite typical of that so often seen in chronic nephritis—the whole disk margin being obscure and numerous hemorrhages and yellow areas being scattered everywhere throughout both retinae. Occasional rises of temperature to 99° and 100° occurred in all cases, but temperatures of 101° and 102° were only recorded with complications, as tonsillitis, phlebitis, and conditions simulating trench fever.

Well-marked blood changes may take place in this group. The hemoglobin was often reduced to 50 per cent. As the red blood corpuscles were not proportionately reduced, the color index was below unity. Unless a secondary infection was present, there was no leucocytosis. Differential counts showed that the polymorphonuclear leucocytes were relatively reduced, while the large mononuclear hyaline cells were relatively increased.

Routine urine examination. The specific gravity was usually low during the period of diuresis or polyuria. Subsequently in half these cases the specific gravity remained at 1.013 to 1.017 until discharge; on the other hand, in five cases it tended to fall and become fixed at 1.010 to 1.012 regardless of the daily amount of urine excreted. This continued inability to eliminate a urine of normal concentration suggests permanent renal damage. The amount of albumin in the urine decreased in nine cases, though on discharge the amount varied between a trace and 1.2 per cent. In one case it remained stationary at 0.7 per cent throughout. This diminution in the albumin usually coincided with improved renal function, but in several instances a small amount of albumin was accompanied by a poor excretory ability. The periodic appearance of gross blood in the urine was typical of these cases. Macroscopic hematuria was more or less persistent in six cases; its presence was not incompatible with moderately good renal function. With the

appearance of gross blood there was an apparent decrease in the number of casts. This decrease was more apparent than real, as on laking the red blood corpuscles many casts could be observed in fields where previously none had been seen, the red cells having overlain and hidden the casts. It was remarkable that with marked hematuria blood-casts were very rare. On macroscopic examination red blood corpuscles, polymorphonuclear leucocytes, and large mononuclear cells often containing blood-pigment were found in all of these cases. The presence of microscopic pus definitely arising from the kidney itself was demonstrated in one case by means of ureteral catheterization.

Functional studies. More marked and varied changes were revealed in these cases than in the resolving group. Distinct fluctuations in the ability of the kidney to excrete phenolsulphonephthalein, urea, and chlorides were characteristic, though very often one substance might be very well eliminated whilst another was retarded. In table 2 these variations are given in detail. All of the ten cases at some period while under observation showed a diminished phthalein excretion—the amount varying from 10 to 50 per cent. Two cases, which on admission excreted 32 to 38 per cent, gradually improved and before evacuation had an output of 62 to 64 per cent. Two, more serious cases, showed weekly fluctuations, but on discharge eliminated only 18 to 22 per cent. On the other hand, in five cases with an initial excretion of 45 to 55 per cent there was a tendency for the excretion to remain at this level or decrease slightly with apparent general recovery. The urea content of the blood was definitely increased, 77 to 158 mgm. per 100 cc., in seven of the ten cases, while in an eighth patient a total non-protein nitrogen of 87 mgm. indicated a heightened blood-urea content. In two cases the blood-urea content was within normal limits during the patient's stay in hospital. This increase in the urea in the blood was more marked and occurred in a much higher percentage of cases than in the previous type. The blood-urea was found increased more frequently in the early stages of the disease though a high-blood urea content was not limited to any particular period. When the total non-protein nitrogen was

determined on the same specimen of blood in these cases of retained urea, the urea nitrogen averaged 63 per cent, but when, on the other hand, the total urea was within normal limits, the urea nitrogen averaged 48 per cent. Ambard's coefficient was determined at different periods in eight of these cases, and in every case the resulting index was above the normal. On discharge, in four cases Ambard's coefficient varied between 0.098 and 0.165.

The concentration of chlorides in the plasma was initially high in six cases, and subsequent estimations revealed results similar to those in the resolving group. In two cases the chlorides gradually fell to normal, while in the other four there was a decrease during or immediately after diuresis, with a later rise and a final fall to the normal level. The plasma chloride content was normal or only slightly elevated in one case during his stay of seven weeks in the ward. In an eighth case the chloride content was normal on admission, but later became high and remained so until discharge. This was associated with a low chloride concentration in the urine. The most interesting case in this series with regard to chloride metabolism was W. V. On admission the plasma chlorides amounted to 624 mgm. per 100 cc. During the next three weeks the edema increased, water and chlorides were excreted in small amounts, and at the end of this period, the chlorides in the plasma had reached the low figure of 490 mgm. per 100 cc. Later, following an increased elimination of chlorides and water in the urine, the plasma chloride content rose to 600 mgm. per 100 cc. Thus a marked retention of chlorides in the tissues was associated with a plasma chloride content 12 per cent below the generally accepted threshold.

The excretion of chlorides in the urine was often diminished, as one might expect from the slow disappearance of edema and tardy onset of increased urinary output. Early in the disease four cases had both a low concentration and a low total output, although the plasma chlorides were above the threshold. With improvement in clinical condition and renal function, the chlorides were well excreted. Three of these cases were given the

sodium chloride test before discharge—one excreted the extra chloride exceedingly well, while the other two had a fair concentration, but failed to eliminate the total quantity. In four cases the chloride concentration and total output were normal throughout their stay in hospital, and the final extra salt was well excreted with the exception of one case. The remaining two cases, S. H. and J. K., showed fluctuations in all excretory functions, including the chlorides. These changes were due to mild relapses. Both these cases failed to excrete satisfactorily the additional chloride given before discharge.

Acid-base relationship. There was evidence of a diminished alkaline reserve in nine of the ten cases. In all probability the remaining case, W. V., would have shown a similar condition, but alkali had been administered shortly after his admission to the casualty clearing station and subsequently while at the base. The alkali reserve of the plasma was estimated in a number of these nine cases on a specimen of the blood taken at the same time as the alveolar CO_2 tension was determined. For convenience the results obtained will be described together. On admission, in all of the nine cases, the alveolar CO_2 tension varied between 23 and 35 mm. Hg; in five the RpH between 7.8 and 8.2, and in four the combined CO_2 was 37 to 47 cc. Thus it will be seen that the initial acidosis in these cases, though still moderate in degree, tended to be slightly more marked than in the resolving group. Two cases only, J. T. and H. W., recovered rapidly without therapy. Two further cases were not given alkali for some time after admission, and a deficiency of alkali reserve persisted. On the other hand, in two other cases alkali was administered early, and within a few days the acid-base relationship became normal, but subsequently, after discontinuing the medication, relapse occurred and the acidosis reappeared. These cases were then given alkali until discharge. Having observed this tendency of the acidosis to persist and also recur, alkalies were given from admission still evacuation in three cases and no return of the condition was manifest. The effect of alkali thereby on the acid-base equilibrium in certain of these cases is tabulated below.

NAME	DATE	ALKALI MEDICATION	ALVEOLAR CO ₂ TENSION	RpH	COM- BINED CO ₂
			<i>mm. Hg.</i>		<i>cc.</i>
A. S...	11/iv	None	25	8.1	
	3/v	None	25		
	6/v	Sodium lactate, grams 4, four-hourly			
	24/v	Sodium lactate, grams 4, four-hourly			
J. K...	2/v	Sodium lactate, grams 4, four-hourly	25	6.8	
	12/v	Sodium lactate, grams 4, four-hourly	38	8.2	
	27/vi	Discontinued			
	16/vii	Relapse	28	8.1	39
	16/vii	Sodium bicarbonate, grams 4, four-hourly			
W. G.	23/vii	Sodium bicarbonate, grams 4, four-hourly	40	8.3	73
	23/viii	Sodium bicarbonate, grams 4, four-hourly	28	7.9	37
	28/viii	Sodium bicarbonate, grams 4, four-hourly			
	4/ix	Sodium bicarbonate, grams 4, four-hourly	39		59
	3/x	Sodium bicarbonate, grams 4, four-hourly	43		59

RELAPSES

Cases of war nephritis show a tendency to relapse. In this series eight or over 24 per cent had severe exacerbations of the disease. Often a definite cause, such as an intercurrent infection, was present, but sometimes no causative factor could be demonstrated. We do not include as relapses those frequent recrudescences, marked by a slight fever and by increased blood and albumin in urine, which last only a few days and leave the patient, as far as functional tests show, none the worse.

In two of the eight cases (S. H. and J. K., table 2) the relapse prolonged the ordinary course of the disease. These cases have already been referred to in the non-resolving group. In six the relapse was much more severe than the original attack and caused symptoms so grave that the patients' lives hung in the balance—of these two died and four recovered. It is with the course of these latter four that this section especially deals (table 3).

These four cases arrived at the base on the fourth to the ninth day of illness. All showed moderate signs of bronchitis, only one

C., 34, 12/v/17.....	25	N	Tr.	105	280	1.011	0.40	+	0.14	Tr.	564	90	66	39	8.4																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			
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TABLE 3.—Continued

PATIENT, AGE, DATE OF ADMISSION	DAY OF DISEASE	TEMPERATURE degrees	EDEMA	URINE					PHENOLSTULPHONEPHTHA- LEIN	BLOOD			ACID-BASE RELATIONSHIP			REMARKS
				Amount cc.	Specific gravity	Albumen per cent	Gross blood	Chloride per cent		Chloride mgm. per 100 cc. plasma	Urea, mgm. per 100 cc.	T. N., P. N., mgm. per 100 cc.	Alveolar CO ₂ ten- sion mm. Hg.	RpH	Combined CO ₂ of plasma volume per cent	
W., 27, 9/viii/17....	22	100.8	0	930	1.030	0.50	+ 0.25	50	550	52			40		55	
	23	101.4	0	740	1.025	1.60	+ 0.01	33	559	110			33	7.9	39	
	30	100.8	0	115	1.005	0.10	+ 0.04	33	578	138			35		46	
	39	99.6	0	95	1.006	0.20	+ 0.07									
	48	100	0	95	1.005	0.60	+ 0.12									
	57	99.4	0	100	1.005	0.30	+ 0.25	54	608	41			42		51	
	64	99.4	0	105	1.005	0.30	+ 0.34	60	617	35			40		54	
													0.0920			

had a phenolsulphonephthalein excretion below 50 per cent. For varying periods after admission progress was excellent. The usual diuresis took place with an accompanying flood of chlorides and disappearance of edema. In every case the phenolsulphonephthalein excretion rose to 60 per cent or higher. In no way did their course differ from that of other members of the resolving group, and a speedy recovery was anticipated in each case. Unfortunately, however, in periods ranging from the fourteenth to the twenty-first day of disease each had a severe relapse. This relapse was heralded in each case by a smart rise in temperature to 100° to 103.4° F., by the appearance of gross blood in the urine, by a fall in the urinary output and a return of tenderness on pressure over the costo-vertebral angles. In one case, W., the relapse was due to a staphylococcal epididymitis. This patient gave an indefinite history of venereal infection three years previously. Ten days before the epididymitis developed a urethral discharge had been noticed and his urine became very rich in pus cells. No gonococci could be found and Wassermann's reaction was negative. A second case, E., developed, during the relapse, a phlebitis. In the third case, C., the relapse was attended with severe pains in the shins and ankles, simulating an attack of trench fever. In the fourth case, B., no cause could be found for the relapse.

The urinary output kept low for periods varying from four to thirteen days, but only in one case, C., did the daily amount fall below 500 cc. In this case the output averaged 300 cc. per diem for ten days, falling as low as 150 cc. With this retention of water, in two cases only did edema reappear. This amounted at most to a spongy pad over the sacrum, and never at all simulated the original condition. Although in all these cases there was a marked urea retention, yet in only two, C. and B., did we observe any so-called uremic symptoms. These patients had at times severe headache, some vomiting and vertigo, but never were convulsions or muscular twitchings observed. In the other cases subjective symptoms were strangely absent, at most slight headache and some distaste for food. In no case was there a return of the distressing dyspnea. An interest-

ing clinical feature of these cases during relapse was a fall of systolic blood-pressure from 130-150 to 95-115 mm. Hg. One case, C., developed during relapse two small retinal hemorrhages. No eye-ground changes were observed in the others.

Routine urine examination. With the relapse there was always a sharp fall in the amount of urine. The urine was colored dark red with blood. This gross hematuria lasted from one to seven weeks. In the case, B., in which the colour of the urine cleared in a week, the hematuria returned at intervals.

In two cases (C. and W.) the specific gravity showed a marked rise as the quantity of the urine fell. When diuresis was established the specific gravity fell and remained at a low level until evacuation from hospital. In one case (E.) the specific gravity steadily fell and remained low; the urinary output in this case had never fallen below a litre and the diminution was transient. The specific gravity of the fourth case (B.) did not vary. The amount of albumin always showed a rise at the beginning of the relapse; but if the urine output continued low there was a secondary fall.

Functional studies. An absolutely constant finding was a very sudden drop, not only in the total output of chlorides but also in the chloride concentration of the urine. This fall accompanied the decrease in the amount of urine. In two cases (C. and W.), the day previous to the relapse, and while the output of the urine was still at a high level, there was a sharp rise in chloride concentration in the urine. This preliminary rise previous to a drop was noticed several times in other cases of milder relapses. Long after the amount of urine had risen to its original level this low chloride concentration continued, and lasted for periods ranging from four to seven weeks, and in one case (E.) was still low when the patient left hospital eight weeks later. Thus no avalanche of chlorides, so striking a feature in the non-resolving group, followed the re-establishment of urinary output after a relapse. The response to the extra salt test was a sharp rise in three cases of the chloride concentration of the urine and the extra salt was well eliminated. The fourth case (E.), whose chloride concentration in the urine had remained persistently low since relapse, failed to eliminate the additional salt.

In only one case (C.) did we closely follow the excretion of urea. This remained at a low total during the period of low urinary output, but the concentration kept at a fair level. With the establishment of diuresis the total excretion of urea rose *pari passu* with the excretion of water.

Before the relapse all four cases were excreting 60 per cent or over of phenolsulphonaphthalein. In two (C. and B.) it fell at once to a mere trace, not estimable; in a third (E.) to 20 per cent and later to 14 per cent. In the fourth case (W.) the fall was slower, at once to 50 per cent, and a week later the figure was still further reduced to 33 per cent. This case a month later had again risen to 60 per cent, while the other three were still under 40 per cent. on departure from hospital, six weeks to two months after the relapse.

In all four cases there was a marked retention of urea, the urea content of the blood varying from 93 to 220 mgm. per 100 cc. of blood. The highest blood urea content was reached in from six to seventeen days after relapse, and the fall to normal was much more gradual, taking from eighteen to fifty days. One case (E.) still showed a figure of 56 mg. per 100 cc., with an Ambard's coefficient of 0.124, on leaving hospital seven weeks after relapse; while C., although blood urea was within normal limits, still showed an Ambard's coefficient of 0.116 on evacuation.

In only one of these cases during relapse did the plasma chloride content deviate from the normal figure. This was in Case C., in which a low urinary output had lasted for thirteen days. Here the plasma chloride content fell from 631 mgm. per 100 cc. to 418 mgm., but with the establishment of a diuresis it rose quickly again to 612 mgm.

Acid-base relationship. During relapse two cases received sodium bicarbonate, 4 grams every four hours, with the result that little tendency towards acidosis was manifested. For example, C. in the third day of his relapse had an alveolar CO₂ tension of 39 mm. Hg. and RpH 8.4, and on recovery from relapse the figures were 42 and 8.4. On the other hand, two cases did not receive alkaline medication, with the result that during relapse distinct evidence of an acidosis developed; Case B.

showing an alveolar CO_2 tension of 28 mm. Hg. and an R_pH value of 7.9; Case W., alveolar CO_2 tension 33, R_pH 7.9, combined CO_2 39 cc. In both cases acidosis disappeared, in one with and in the other without the assistance of alkali therapy.

ACUTE INFECTIVE NEPHRITIS

In the mode of onset, development, and further course, two cases of acute nephritis resembled closely an acute infection. Both were young soldiers, aged nineteen and twenty-four, who reported sick with a definite localized infection, one with an otitis media involving the mastoid, the other with a diffuse infection of the right foot. A week to ten days later symptoms of nephritis were present. Operative treatment was instituted after the nephritis had developed, and in spite of good drainage and improvement in the local condition, high temperature and severe headache continued for two to three weeks. Following operation both cases were transferred to the nephritis ward and renal functional studies were commenced. Subjectively headache, fever, and costo-vertebral tenderness were the chief complaints. Edema was very slight and limited to the face. Dyspnea was not present. The disappearance of the edema within a few days was not associated with a definite diuresis. The blood-pressure remained low—100 to 110 mm. Hg. during the period of high fever, rising to normal with convalescence. The eye-grounds were normal in one case, while the optic neuritis, noted in the case of otitis media L., was considered to be due to increased intracranial pressure.

Routine urine examination. The specific gravity ranged in one case between 1.010 and 1.016 throughout. In another the specific gravity averaged 1.010 during the fever period, but later at the end of a month reached 1.014. Albumin was present in moderate amount, but decreased rapidly from 0.12 per cent to a trace. Macroscopic blood was present during the fever period along with white blood corpuscles, large mononuclear cells and numerous casts. With general improvement the casts became scanty but red blood corpuscles and the large mononuclear cells still persisted.

Functional studies. The excretion of phenolsulphonephthalein was definitely diminished, being as low as 40 per cent in both cases and on discharge amounted to 45 to 50 per cent. The most striking functional disturbance was the high urea content in the blood, reaching 109 and 154 mgm. per 100 cc. with a corresponding increase in the total non-protein nitrogen. That this increase of urea in the blood was largely due to insufficient elimination was clearly indicated in one case by a high Ambard coefficient of 0.478. With the fall in temperature and general clinical improvement the blood urea rapidly fell to normal, although the phenolsulphonephthalein output was still somewhat reduced, 45 to 50 per cent. In the case associated with otitis media Ambard's coefficient was normal, 0.075, before discharge. The chlorides in the plasma amounted in one case to 639 mgm. per 100 cc., but otherwise showed nothing abnormal. In the urine the chloride concentration remained low during the fever period, while on discharge the extra chloride was well eliminated.

Acid-based relationship. A slight but definite degree of acidosis was demonstrated in one of the two cases as shown by an alveolar CO_2 tension of 28 mm. Hg. Plasma withdrawn at the same time showed a slight reduction in the alkali reserve, R_pH being 8.1, and combined CO_2 49 cc. With improvement in the patient's clinical condition the acidosis quickly cleared up.

FATAL CASES

The results of clinical and functional studies carried out on seven cases which subsequently died are given in table 4, while detailed pathological findings in six of these cases are described below. One case was evacuated to England ten days before death, and during this latter period was under careful observation in St. Bartholomew's Hospital, London.³ These patients varied in age from twenty-two to thirty-three years, and as far as could be ascertained were all in robust health before the onset of acute nephritis.

³ We are indebted to Lt.-Col. J. Calvert for the notes and chart of this patient while under his care.

Two of these cases ended fatally at the end of the second week from onset. Both had moderate general edema, a raised blood-pressure, and passed a urine of specific gravity of 1.020 containing a heavy cloud of albumin and many casts, white and red blood corpuscles, but no gross blood. Complete functional studies were not made because at that time we had not procured all the necessary laboratory equipment. Patient J. G. was admitted on the seventh day of disease and appeared to be progressing satisfactorily; for four days his daily urinary output varied between 1600 and 2200 cc. on a fluid intake of 2 litres, and during this period 50 per cent of phenolsulphonephthalein was excreted in one hour. Forty-eight hours before death he began to vomit frequently, and on the following day had repeated severe general convulsions. He remained in a comatose convulsive state till death. Respiration during the last twenty-four hours was deep, laboured, but regular, and the temperature did not rise above 100°. Patient P. R. was admitted somewhat later in the disease—the twelfth day—and soon severe vomiting along with Cheyne-Stokes respiration developed. At this time the alveolar CO₂ tension was 25 mm. Hg. Later, convulsions developed, and coma persisted until death on the fourteenth day. A few hours before death the phenolsulphonephthalein excretion amounted to 10 per cent.

An infective process in addition to the original nephritis appeared to be the immediate cause of death in two cases, R. B. and C. M., on the thirty-fourth and seventeenth day of illness respectively. In spite of the continued edema the output of urine was considerable, and the chloride concentration fair up to the time when phlebitis and staphylococcal septicemia respectively developed. Renal excretion rapidly diminished as the infective process progressed, and in a few days the patient succumbed. During this latter period vomiting, severe headache, and mild delirium were present, but no convulsions. Both cases showed a high degree of urea retention. Acidosis was moderate in degree. One case failed to excrete phenolsulphonephthalein.⁴ Both of these cases showed retinal hemorrhages,

⁴ A phenolsulphonephthalein test was not carried out in case C. M. on account of the difficulty in catheterization due to a prostatic abscess.

and one an area of degeneration without any abnormality being noted in the optic disk or its margin.

Three cases with severe symptoms on admission and showing little or no improvement when subjected to the routine therapeutic measures were non-resolving in type. Unlike the favorable cases that later recovered, the edema persisted, general anasarca gradually became more marked, and a diuresis or polyurea did not develop. The course of the disease, forty-five and fifty-two days respectively, was characterized by a gradual rather than a sudden decrease in renal function. The blood-pressure was initially raised, but fell with the development of terminal symptoms. Retinal changes were limited to several small hemorrhages in two of the cases. From the time of admission the secretion of phenolsulphonephthalein was very small, a trace to 5 per cent. The total output of chlorides was low, and the urea in the blood high (indicated in two cases by increased total non-protein nitrogen). An acidosis accompanied these indications of severe renal insufficiency. The relationship between the chloride concentration in the plasma and urine was of particular interest as the disease progressed. In case F. G. the initially high plasma chloride content decreased during the terminal period, but never fell below the normal threshold of 560 mgm. per 100 cc., while the concentration in the urine continued to be relatively high. On the other hand, in two cases the plasma chlorides fell to a figure well below the normal threshold, and at the same time the chloride concentration of the urine became extremely low.

The terminal stages of the disease were marked clinically by oliguria, headache, vomiting, orthopnea, bradycardia (in two cases,) muscular twitchings, and final coma. In addition to these symptoms, B. had a single general convulsion. The respirations were always rapid, labored, irregular at times, but the Cheyne-Stokes periodic type was not observed. There was no definite terminal rise in temperature, and the slow heart rate, thirty-two to the minute in F. G. a few hours before death, was striking. Complete anuria was never present, even post mortem the bladder always containing 100 cc. or more of urine.

PATHOLOGY

Our pathological data were obtained from six fatal cases whose clinical and functional histories have been already described. Of these two died in the second week and two in the seventh week of the disease. In two death was due to an intercurrent infection.

The two acute cases died on the thirteenth and fourteenth days respectively of illness. Histological examination showed features so similar to those described by Dunn and McNee (11) in a recent article that a detailed description need not be given here. Briefly the most important changes (figs. 1 and 7) are enlargement and swelling of the glomeruli with marked increase in the nuclear elements. Nuclei in the process of mitotic division are not uncommon. Protrusions from these swollen glomeruli into the aperture of the proximal convoluted tubule are frequently seen. There is a marked absence of red blood corpuscles in the capillaries of the Malpighian tuft due to the blockage of these vessels by an accumulation of large mononuclear cells. Catarrhal changes and hyaline droplets are present in the epithelium of the convoluted tubules, while the epithelium of the collecting tubes shows less damage. Hyaline casts, numerous in one case, are found in the junctional tubules. In the second case casts are only found with difficulty. Intratubular hemorrhage is marked in both cases in the tubules adjacent to the arteriolae rectae. The interstitial tissue is not increased in amount.

Both of the fatal cases in the non-resolving group were young men of twenty-two and twenty-six years of age, and death occurred on the forty-fifth and fifty-second day of illness. Post-mortem examination showed the following naked eye appearances. Anasarca is general and the pleural and peritoneal cavities contain a large excess of fluid. The fluid in the pericardial sac in one case is not increased. The kidneys are enlarged, weighing from 225 to 260 grams each.

The capsule still strips readily. Subcapsular mottling is very marked. Fresh bright red and older purpuric spots of

haemorrhage are intermingled with pale areas of degeneration. On section the cortex is bulging and swollen, paler and duller than usual, and mottled. Standing out as white translucent glistening dots the glomeruli at once attract attention. The course of the straight vessels is rendered very distinct owing to their congestion. The beefy tint of the pyramids contrasts strongly with the pallor of the cortex.

The heart is dilated but not hypertrophied. A few petechiae are present in one case under the endocardium of the left ventricle.

The lungs are voluminous, markedly congested, and edematous. In one a definite area of red hepatization is present in the left upper lobe.

The liver is enlarged and congested. In one instance pale areas are scattered throughout the liver substance. These histologically proved to be areas of polymorphonuclear infiltration around the intralobular veins.

In one case the spleen is slightly enlarged, in the other it is markedly atrophic. In both subcapsular hemorrhages are present. Hemorrhagic areas are present in one case in the caecum. The hemolymph glands of the abdomen in one case are universally enlarged and bright pink in colour. The suprarenal capsules and pancreas show no gross change. The brain is edematous, but in neither case are hemorrhages observed.

The histological changes (figs. 3, 5, and 9) in these two kidneys are similar and in their evident character in sharp contradistinction to the acute cases. The majority of the glomeruli show an extensive and progressive proliferation of the endothelial cells lining Bowman's capsule. This results in a laminated thickening gradually filling up the lumen. Generally this thickening is arranged as a crescent with the horns pointing towards the pedicle of the tuft and the thickest part occluding the aperture of the convoluted tubule. Around the glomeruli there is a marked increase in connective tissue formation, and fine fibrils of fibrous tissue can be traced radiating outwards between the adjoining tubules, or passing inwards through the pedicle into the tuft. The tuft itself shows thickening of the walls of its

capillaries with marked fibrous change in the supporting connective tissue. Adhesions take place between this altered tuft and the thickened capsule; these adhesions, together with the contraction of the fibrous tissue in the tuft, produce marked lobulation. All stages in this destruction of the glomeruli can be seen up to complete sclerosis. There is a very definite overgrowth of the interstitial tissue. This is especially marked in the cortex around the glomeruli and blood-vessels, where small round-celled infiltration is also evident. The connective tissue often runs in definite strands. The increase is much less marked in the pyramids where the interstitial tissue is much less dense and markedly edematous.

Degeneration of the tubular epithelium is widespread and severe in degree. Some tubules are obstructed by the overgrowth of connective tissue; others are widely dilated and edematous. The cells are swollen, irregular in outline, with faintly staining nuclei. Hyaline droplets in the cells of the convoluted tubules are of frequent occurrence. Sections of the walls of the tubules are often denuded of epithelium and the degenerated cells lie loose in the lumen. In one case hemosiderin is present in many of the epithelial cells of the convoluted tubules. Many of the tubules are filled with strongly eosin-staining hyaline material, and others contain granular debris in which are embedded the remains of degenerated nuclei. Intratubular hemorrhage is a very striking feature and polymorphonuclear leucocytes are of not infrequent occurrence. Many tubules contain the large mononuclear cells whose presence in the urine is so striking. These cells correspond histologically with the large mononuclear cells seen plugging the capillaries of the Malpighian tuft in the early cases as described above. The origin of these cells is doubtful, but we are inclined to regard them with Mallory (12) as being the large mononuclear leucocytes, or, as he prefers to call them, endothelial leucocytes, and are probably derived from proliferation and desquamation of the endothelial cells lining the capillaries. It is interesting to note in this connection that, as already described, we have seen a relative increase of the large mononuclear leucocytes in the blood in the non-resolving group.

One of the two fatal cases whose death was due to an intercurrent infection was a non-resolving case who died on the thirty-fourth day of illness. This case (R. B., table 4) had been making good progress clinically until he developed a phlebitis of his left median basilic vein. Gross pathological changes were very similar to those above described, but the kidneys were larger and softer. Bacteriological examination of the thrombus post mortem gave negative results. Histologically (figs. 2 and 4) this kidney showed features intermediate between the early and late types detailed above. The glomeruli are now somewhat shrunken, and marked fibrous thickening has taken place in the supporting tissue of the capillaries, especially in the pedicle. Contraction of this tissue has produced distinct lobulation of the tuft. The accumulation of mononuclear cells is not so marked in the capillaries. The cells lining Bowman's capsule show proliferation of their nuclei, but only in a few glomeruli could distinct lamination be seen. The tubules are separated by a large amount of young and very edematous connective tissue. The epithelium of the convoluted tubules is uniformly flattened. Cast, blood, and mononuclear cells in large numbers, are present in many of the tubules. There is a very marked small round-celled infiltration of the interstitial tissue, especially around the glomeruli and blood-vessels.

The second fatal relapsing case (C. M.), whose death was due to a staphylococcal septicemia originating from a prostatic abscess, died on the seventeenth day of illness. The gross appearance of the kidney is similar to that described above, except that the cortex is darker and a few small pyemic areas are present along the course of the vessels in the cortex. The two kidneys together weigh 585 grams. Histologically (fig. 6) sections show, in addition to the features seen in the acute type, a marked exudation of blood and polymorphonuclear leucocytes into Bowman's capsule. The resulting fibrin forms a thick layer inside Bowman's capsule, and can often be seen plugging the neck and extending some way into the proximal convoluted tubule. This is accompanied by proliferation and desquamation of the capsular endothelium. All the blood-vessels

are widely dilated and congested with blood. The tubules contains much blood and many polymorphonuclear leucocytes. Hyaline and granular casts are fairly numerous. Mononuclear cells are rare. The lining cells of the tubules show marked cloudy swelling and hyaline droplet formation. The interstitial tissue is markedly edematous and infiltrated with polymorphonuclear leucocytes.

We have had the opportunity of examining the kidneys of a case (J. D.) which died on the thirty-first day of the disease, under the charge of Capt. J. M. McCloy and is not included in our series. The course of the disease was steadily downward and was not complicated by any intercurrent infection. The kidneys are soft, friable, and greatly enlarged, weighing together 620 grams. Apart from their large size and consistency, naked-eye appearances are similar to those described in the cases dying later in the disease. Histologically sections closely resemble those of R. B., already described, except that the glomeruli are not shrunken and lobulation has not taken place (fig. 8). Proliferation and desquamation of the cells lining Bowman's capsule are present. In many glomeruli this only amounts to a multiplication of the nuclei. Crescent formation has not taken place. The increased size of the kidneys is due to the intense interstitial edema. Small round-celled infiltration is present around the glomeruli and blood-vessels. The epithelium of the convoluted tubules is uniformly flattened and mitotic division of their nuclei is not uncommon. These two cases (R. B. and J. D.) show in every respect an intermediate stage in the progress of renal change between the cases dying in the second week of the disease and those in which death was delayed until towards the end of the second month.

In none of the cases described above did we find any histological evidence pointing to a previous renal lesion.

PROGNOSIS

In discussing the further course of these cases it must be remembered that this series was specially selected from the severest cases entering our ward. In general, the cases of the resolving

type progressed satisfactorily while at the base. On evacuation they were free from edema, had a normal blood-pressure, and good renal function, although albumin and cylindruria were still present. Subsequent reports from medical officers in England showed that recovery was slow—all the cases were still in hospital from two to four months after onset. Three cases were discharged within four months fit for further service. The only patient included in the series who had a previous attack of war nephritis ran a very favorable course, and at the end of the three months his urine was free of albumin. It is interesting to note that this is one of the three cases so far reported to us in which the albumin had cleared up. Such facts would indicate that even with early satisfactory progress, prognosis as to final recovery must be guarded.

As was to be expected from the protracted early course of the non-resolving cases, recovery was delayed. Though nine out of the ten patients on evacuation were edema free and had a normal blood-pressure, none of them had strictly normal renal function. There was always a definite secondary anemia, a tendency to periodic hematuria, and later, in England, the edema reappeared in the dependent parts when the patients were allowed to walk. All of the non-resolving cases were still in military hospitals four to seven months after onset.

As previously mentioned, the occurrence of a relapse was of serious import. In the subsequent course of the four cases studied the condition improved slowly and resembled closely that seen in the non-resolving type. One case remained in hospital for nine months. We have no record of any of these non-resolving and relapsing cases being discharged fit for even light duty.

Our fatal cases represented a total mortality of 2.3 per cent in 300 cases. Death may occur at any stage. In the early course of the disease fatal symptoms may arise suddenly, unforeshadowed by any marked derangement of kidney function. However, in the non-resolving group, grossly impaired function of a progressive nature may herald a fatal prognosis several weeks before death, recalling the slow and lingering termina-

tion of the chronic nephritic. Intercurrent infection at any time during the course of the disease was always of serious prognostic significance.

TREATMENT

In the early stages of the disease the patients were given a milk diet restricted to 1800 cc. Though this was not a strictly low protein diet, no increase in the blood-nitrogen was observed to follow its use. Of more importance from a dietetic point of view was the limited intake of fluid and chlorides while edema was present, owing to a retention of these substances in the body. In severe cases the edema definitely increased in spite of the low intake. Von Noorden (13) has emphasized that in acute nephritis it is quite useless to give the patient large quantities of fluid in order to flush out the kidneys, as this only unnecessarily irritates an organ which is already incapable of excreting water. Widal and Lemierre (14) have shown how the administration or suppression of salt in the diet could determine the appearance or disappearance of edema. After the retained substances had been excreted a more liberal diet, containing 4 grams of chloride and 15 grams of nitrogen, was permitted. No untoward results were observed to follow this increase in diet.

Because of MacNider's (15) demonstration that the administration of alkalies previous to the production of experimental uranium nephritis lessened the extent of the renal lesion, and also because a mild acidosis was present in many of these cases, alkali therapy was given a rather extensive trial. Three cases which did not seem to be progressing satisfactorily showed distinct improvement in renal function after the giving of alkali, sodium bicarbonate or sodium lactate, 4 grams every four hours, for a period of seven to ten days. On the other hand, cases which received no alkali did extremely well. Again, several cases received alkali in the above amounts for weeks, but showed no definite improvement. One case (C., table 3) was given bicarbonate previous to and during a serious relapse without apparent effect. That a diminished alkali reserve could be quickly restored by the use

of alkali was strikingly demonstrated in the fatal case J. B. (table 4). On admission the combined CO_2 of the plasma was distinctly decreased. With the administration of sodium bicarbonate, 4 grams every four hours, the reserve of the blood became normal and the urine alkaline within four days. This condition was maintained throughout the remainder of his illness without any evident beneficial effect on the symptoms or course of the disease. Twenty grams of bicarbonate in 5 per cent solution injected intravenously in three cases of oliguria failed to produce an increase in the urinary output. Persistent oliguria proved to be a serious therapeutic problem in six cases. Three hundred and fifty cubic centimeters of 5 per cent glucose given intravenously failed to increase the amount of urine. A negative result likewise followed the use of a 10 per cent solution in a second case. Theobromine (0.5 gram every eight hours for four doses) was employed in four of these cases. In one an immediate and persistent diuresis followed the use of this drug, while in the other no benefit was observed. For the treatment of convulsions, morphia, venesection, and lumbar puncture all appeared to be helpful, although in three cases, subsequently fatal, none of these measures had more than a temporary effect. Hot packs were employed as a routine measure in all cases of persistent edema; of their utility, however, little evidence was obtained.

DISCUSSION

The term war nephritis has been employed to include several forms of renal disease. In the present investigation the term has been limited to those acute cases which showed an abrupt onset with symptoms of dyspnea and edema. We have described a so-called infective acute nephritis, which from the mode of onset and general course would appear to be quite distinct. A similar condition was described by Ameuille (16) as a type of war nephritis to illustrate the rôle of infection as an etiological factor in the production of this condition. We have included these cases in the present study in order that they might be distinguished from the typical cases of war nephritis.

From the beginning of this investigation, it seemed clear that although the majority of cases of war nephritis, even with marked initial symptoms, rapidly improved when put to bed and given a limited diet, yet others failed to respond to any of the usual methods of therapy. These two groups can be distinguished clinically and functionally. Whether the second or non-resolving group is a sequel of the first or only a more severe manifestation of the disease from the onset is difficult to determine. One fact is clear, however, that the non-resolving cases have a greater tendency to pass into a condition simulating chronic parenchymatous nephritis. The main distinguishing features of the two groups may be summarized as follows:

Resolving type. These cases arrived at the base relatively soon after the onset of illness and were detained there a shorter time than the non-resolving type. During their stay very marked improvement occurred in their condition, a well-marked diuresis took place early in the disease, and was accompanied by the disappearance of headache, dyspnea, etc. The blood-pressure fell rapidly. Retinal changes were infrequent, slight, and transient. Gross hematuria was rare and did not persist. Albumin and cylindruria decreased rapidly, and the specific gravity of the urine tended to rise to its normal level. All showed a good phenolsulphonephthalein excretion, and the initial rise in blood-urea content quickly fell and remained low. Ambard's coefficient on evacuation was frequently normal. Chloride elimination by the urine was good. Acidosis tended to be slight, and the acid-base relationship was restored without alkali therapy.

Non-resolving type. Cases belonging to this group arrived at the base later in the disease and were detained there longer. Onset of diuresis was delayed, edema tended to remain stationary or even to increase, marked secondary anemia developed, and exacerbations of the disease were of common occurrence. Retinal changes were more frequent and permanent in character. Gross hematuria was a marked and persistent feature. Albumin and cylindruria did not clear up, and the specific gravity of the urine tended to remain low.

Phenolsulphonephthalein excretion was diminished; the initial blood-urea content was higher, its fall much slower, and its subsequent course uncertain. On evacuation none of those examined showed a normal Ambard's coefficient. Elimination of chlorides in the urine was often poor and concentration low. Acidosis was more marked and persistent and alkali therapy was required to restore the acid-base balance.

Acute infective nephritis. This type of acute nephritis always followed a focus of infection already established in the body. Onset occurred with marked fever. Dyspnea was absent and edema was limited to slight swelling of the face. Gross blood was always present in the urine, but albumin was moderate in amount and quickly fell to a mere trace. The blood-pressure was low and never rose above 120 mm. Hg. There was no diuresis or marked polyuria during the stage of improvement.

Phenolsulphonephthalein excretion remained relatively high, but there was a very marked urea retention and an elevated Ambard's coefficient. The urea figure in the blood quickly fell to the normal level and remained low, and on evacuation Ambard's coefficient in the one case examined was normal. Acidosis was present, but mild in degree.

In one of the severe relapses (W., table 3) already described, where the relapse was due to a staphylococcal epididymitis, the symptoms were comparable to an acute infective process. Fever was high and prolonged; phenolsulphonephthalein excretion did not fall to a marked degree; the urea in the blood quickly fell, and on departure from hospital Ambard's coefficient was only slightly above normal. Thus here we had a condition of acute infective nephritis grafted onto a typical case of war nephritis.

Certain phenomena occurring in this disease are of great importance from an etiological and therapeutic standpoint. These will now be discussed in relation to our functional and pathological results.

Dyspnea. Dyspnea has been recognized as a common and distressing feature in war nephritis. A history of its presence at onset was given by all our cases, while on admission

75 per cent of the patients still complained of respiratory distress. Bronchitis, pleural effusion, and congestion of the lung bases were undoubtedly often causative factors, yet certain cases had dyspnea without pulmonary signs that could be distinguished clinically. This latter group suggested the possibility that the condition might be due to an altered acid-base relationship in the circulating blood. Although an acidosis was demonstrated in a majority of the dyspneic patients the condition was never as severe as that encountered in terminal chronic nephritis. With regard to the relationship between dyspnea and acidosis in those cases free from clinical signs in the chest, three groups could be distinguished: First, dyspnea associated with an acidosis sufficient to cause respiratory symptoms; this occurred in two fatal cases and two with recovery. Second, cases with dyspnea and a slight or moderate degree of acidosis, which was not severe enough to give rise to respiratory symptoms. Third, cases without dyspnea but showing a moderate acidosis. The natural conclusion from such evidence is that the degree of acidosis existing in the majority of these cases is not the main etiological factor in the production of dyspnea.

Hematuria. Every case examined showed the presence of blood in the urine. This might on the one hand be microscopic in amount, or on the other might color the urine a deep red tint. All gradations between these two extremes were present. This hematuria was often persistent, intractable to treatment, and showed a marked tendency to recur. The coagulation time of the blood in these cases when tested by Wright's method (17) was not delayed. The exhibition of calcium salts did not affect the bleeding. Many cases of war nephritis showed marked pathological changes in their blood-vessels. Three of our cases developed phlebitis. Another case had subcorneal hemorrhages. In the non-resolving group retinal hemorrhages were not infrequent. Post mortem, hemorrhagic areas were found in the endocardium, in the stomach and caecum, and in the spleen. None of our cases showed any miliary cerebral hemorrhages. Histologically the earliest change in the kidneys was found in the delicate vessels of the glomerular tuft and intratubular hemorrhage was marked in all stages.

After the injection of phenolsulphonephthalein gross blood was noted several times in the urine. That the color was not due to the residue of phenolsulphonepathalein in an alkaline urine was proved by counting the corpuscles in a specimen before and after the employment of this dye. In cases characterized by a hypersensitive kidney which tends to bleed at the slightest provocation this test is contraindicated. In the great majority of cases its use produces no ill effects. This tendency to bleed after the employment of substances foreign to the organism for diagnostic purposes has already been described in regard to indigo carmine by Trémolières and Caussade (18), and in regard to lactose by Trevan (19).

Edema. The fact that a patient found himself unable to put on his boots some morning, or that a comrade noticed his feet swollen, was often the cause of his reporting sick to the medical officer. The most frequent seat of edema was in the face, especially around the eyes, and over the sacrum and lumbar region. Edema was also often present over the shins and around the ankle and instep. Edema was sometimes more marked on one side than on the other. Small accumulations of fluid at the base of the pleural cavities were common, yet ascites, penile and scrotal edema were only found in severe cases of the non-resolving type. Edema might pass off quickly in a few days or might persist for three months or more. Disappearance was accompanied by a diuresis and a greatly increased excretion of chlorides. It was apt to recur when the patient was allowed to get up and move about.

The onset of edema is so sudden that it is difficult to imagine that renal retention of water and chlorides is its primary cause. Edema did not reappear to any marked extent in those severe relapses where chloride retention was a marked feature. Again in one of the relapsing cases (C., table 3), a marked chloride and water retention was accompanied by a fall of chloride concentration in the plasma well below the normal threshold. This, with a corresponding fall in hemoglobin, pointed to a condition of hydremia yet without marked edema. The degree of acidosis found as early as the fifth day in the case of K. A. (table 1)

might suggest that acidemia was the causative factor of edema. The findings in certain cases, however, tend to negative such a conclusion. In two cases, although severe edema was present, yet both had a normal acid-base relationship. Again, in Case W. (table 3), during relapse, the recurrence of acidosis was unaccompanied by any reappearance of edema. In several cases of the non-resolving group the exhibition of alkali therapy, although quickly counteracting existing acidosis, yet had no appreciable effect on the edema. In addition, from other evidence, as is shown later, we have come to the conclusion that the acidosis found in acute nephritis is but a secondary phenomenon. Definite pathological evidence has been obtained of toxic action on the blood-vessels. This toxic feature also supplies a reasonable explanation of the onset of edema, which is doubtless later aggravated by the retention of water, salt, and waste metabolic substances within the organism.

Diuresis. Spontaneous diuresis was often the first and surest sign of convalescence. Preceded usually by oliguria, the diuresis soon resulted in the excretion of fluid and other retained substances. A definite and well-marked diuresis occurred in 66 per cent of this series of cases, and much earlier in the resolving than in the non-resolving type. The urinary findings resembled closely the chloride diuresis produced experimentally in animals, though retained substances other than water and chlorides as urea were often excreted. Onset of diuresis might occur early in the course of the disease or be delayed even for weeks. No definite clinical or functional cause was observed for this sudden increase in urinary output. If a definite causative factor for the onset of diuresis could be determined, or a therapeutic agent discovered for its inception, the treatment of many difficult and tedious cases would be simplified. If no relapse follows the diuresis, a good immediate prognosis can be expected.

Convulsions. Convulsive seizures occurred in six cases in this series. Three of these ultimately died; of the remainder, two belonged to the resolving and one to the non-resolving group.

The onset of convulsions as a rule took place early in the

disease. Only in one case (J. B., table 4) did convulsions occur later than the eighteenth day of illness, and in this case took place on the thirty-ninth day, six days before death. In two of the cases there were well-marked premonitory symptoms taking the form of a feeling of numbness and loss of power in the arms. Accompanying this in one case (E. B., table 1), an educated and intelligent man, was a presentiment of impending evil. Two hours later a convulsion occurred. Seizures were of all grades of severity, from twitchings of localized groups of muscles to typical epileptiform fits. In one fatal case these fits were recurrent and severe; in another case (J. N., table 1), who subsequently made a good recovery, six violent convulsions occurred within three hours. The fits in some patients were followed by a condition of hebetude, in others by wild delirium. The persistence of the comatose condition was of bad prognostic significance. Patients making a good recovery woke up after a heavy sleep, with headache perhaps, but with a clear mind and no recollection of what had occurred. Often the contrast between the sane man and the maniac of the day before was most striking. The case E. B. (table 1), whose fit was preceded by a definite aura, noticed that for two days afterwards he had not regained full power in his arms, that he wrote with difficulty, and that his writing was unsteady. The blood-pressure some time after the convulsions was high, as a rule about 180 mm. Hg. In the case E. B., during the prodromal stage the blood-pressure was 150 mm. Hg., but some hours after the fit had risen to 180 mm. Hg. A similar observation is noted by Abercrombie (20). In one case (J. B., table 4) the blood-pressure taken immediately after convulsion had subsided was only 150 mm. Hg.

In two cases at the time of convulsions, the blood-urea was normal in one case (E. B., table 1) and only slightly raised in the second (J. N., table 1). As a matter of fact E. B. had almost normal function at this period. In three cases, as shown by the alveolar CO_2 tension and combined CO_2 of the blood, there was a mild acidosis, but that this was not a causative factor is shown by a fatal case on alkali therapy, whose alveolar CO_2

was 43 mm. Hg. and combined CO_2 of blood as high as 90 cc. In two cases whose cerebro-spinal fluid was examined the hydrogen ion concentration of this fluid was not raised.

Owing to the similarity of these convulsions to those seen in eclampsia, the lipase content of the blood was examined with a view to possible liver involvement (21). In all cases examined, however, the lipase content was normal.

Convulsions are thus seen in every type of war nephritis, in those that terminate fatally and in those that make a good recovery; in resolving and in non-resolving; in those whose renal secretion is good, and in those in whom it is practically in abeyance; in cases showing a mild acidosis and in those saturated with alkali. The occurrence of convulsions is not necessarily of bad prognostic import.

Relapses. Relapses were of frequent occurrence and no type of case was immune. Intercurrent affections, to which these patients were very susceptible, always seem to precipitate a relapse of varying severity. In some instances no cause could be discovered; that some of these idiopathic relapses occurred towards the end of a copious diuresis is suggestive.

Clinically a relapse was marked by a rise of temperature, by the appearance of gross blood in the urine, and by a fall of blood-pressure. Recurrence of edema was slight enough to be easily overlooked. Dyspnea did not recur at all. The functional disturbances attendant on a relapse were much more severe than the clinical symptoms would suggest. There was a marked fall in the excretion of water and of urea, in the chloride concentration of the urine, and in the excretion of phenolsulphonephthalein. The total non-protein nitrogen rose to a high level in the blood and contained a higher percentage of urea than before. With restoration of water output the excretion of urea quickly improved and the blood-urea fell, although Ambard's coefficient remained elevated; but the kidney only very slowly recovered the ability to excrete chlorides and phenolsulphonephthalein.

The acid-base relationship in the blood. The alveolar CO_2 tension was determined in 80 per cent of the cases shortly after

admission. No alkali therapy had been previously given. With a single exception the readings obtained varied between 25 and 35 mm. Hg. These findings indicated an early mild acidosis, and this assumption was confirmed in half the cases by simultaneous estimations of the alkali reserve of the blood-plasma. The methods employed for demonstrating an acidosis, though based on different experimental principles, gave for practical purposes parallel results. In cases that recovered, the acidosis, though definite, was never marked. The lowest values were: alveolar CO_2 tension 23 mm. Hg, R_pH 7.8, combined CO_2 37cc. In one fatal non-resolving case the alveolar CO_2 tension progressively decreased, reaching the low figure of 15 mm. Hg before death. The acidosis was usually less marked in the resolving type, and as a rule disappeared without the use of alkali therapy. When alkali was administered by mouth the urine soon became alkaline and the plasma reserve normal. The fact that in the non-resolving type more alkali was required to maintain the normal acid-base balance in the body pointed to more severe acidosis. Thus the degree of acidosis would appear to be definitely related to the extent and duration of the kidney lesion. This fact, taken with other evidence, shows how closely the acidosis is associated with impaired renal function. The acidosis was always accompanied by retention of substances normally excreted by the kidney, and spontaneous recovery from the acidosis followed the rapid elimination of these substances. We have also demonstrated that an acidosis may occur on two different occasions in the same patient (W., table 3). In this instance there was a deficiency of the reserve alkalinity during the first week, a quick recovery to the normal, but with relapse later a return of the acidosis. These facts indicate that the degree of acidosis met with in cases of war nephritis is secondary to impaired renal excretion. More direct evidence of a deficient acid elimination by the kidney has recently been brought forward by Marriott and Howland (22), who showed that the inorganic phosphates of the blood were increased in certain cases of chronic nephritis in which acidosis is present. We are now investigating the relationship of the inorganic phosphates of

blood and urine in cases of war nephritis, in order to ascertain whether their retention is the important factor in producing the acidosis.

Functional tests. Functional tests must be undertaken in cases of war nephritis in order to secure the best method of treatment and to form a prognostic opinion of any real value. Had we depended solely on clinical observation the gravity of certain cases would have been entirely overlooked.

The phenolsulphonephthalein test gave very valuable information and gave it very quickly. Failure to excrete the dye or to excrete it in more than a mere trace was, with the exception of two very severe relapses, seen only in cases which ultimately proved fatal. Values below 25 per cent were evidence of a very badly damaged kidney and warranted a very guarded prognosis. An excretion between 25 per cent and 40 per cent was characteristic of the non-resolving group and was an indication that progress would be tedious. A reading above 40 per cent was found in all the resolving cases on admission with one exception (J. N., table 1). From a reading above 40 per cent however, one cannot definitely state that the functional powers of the kidney are good. We have found cases with a phenolsulphonephthalein excretion above this which, nevertheless, had a very definite renal impairment, and even one fatal case which had a phenolsulphonephthalein excretion of 50 per cent four days before death. On the other hand, J. N. (table 1), who had a phenosulphonephthalein excretion of only 25 per cent just after a series of convulsions, rose a week later to 60 per cent and showed the marked clinical improvement typical of the resolving group. Widál and his collaborators (23) have shown that in chronic nephritis the excretion of phenolsulphonephthalein gave results parallel to Ambard's coefficient. The work of Rowntree and Marshall, Boyd (24), and Lewis (25) has shown that this is not strictly true in all cases of chronic nephritis. Our results demonstrate that in acute nephritis there is no absolute parallelism between the two. In the early stages of the disease a good phenolsulphonephthalein excretion coexisted with a retention of urea and a high Ambard's coefficient. For instance, A. H. (table 2) showed on the

fifth day of illness a phenolsulphonephthalein excretion of 45 per cent, a blood-urea of 77 mgm. per 100 cc., and an Ambard's coefficient of 0.148, and other instances can be found on reference to the tables. On the other hand, in two of our cases of severe relapse the phenolsulphonephthalein excretion was cut off at once to a mere trace before the urea retention had time to develop; with a return towards normal function the blood-urea content dropped to a normal level, while phenolsulphonephthalein was only 33 per cent. This result agrees closely with the findings of Lewis and Rivers (26) in a case of bichloride poisoning. In cases progressing satisfactorily the blood-urea content dropped rapidly, while the excretion of phenolsulphonephthalein did not show a corresponding rise. As a rule a high phenolsulphonephthalein excretion in the early stages of the disease, even although accompanied by a high urea figure in the blood, was a good prognostic feature.

The estimation of the amount of urea in the blood was of great value, if, in a patient on a known diet, the figure was raised. This gave definite information as to impaired function. A normal figure, however, did not rule out kidney involvement, and it was in this type of case, often accompanied by a good phenolsulphonephthalein excretion, that the estimation of Ambard's coefficient was of great service. As an example of this the following case may be cited. H. W. (table 2); one of the non-resolving group, had a phenolsulphonephthalein excretion of 50 per cent., blood-urea content of 43 mgm. per 100 cc., and an Ambard's coefficient of 0.134. His edema had almost cleared up. A week later edema was absent, phenolsulphonephthalein excretion was 46 per cent, blood-urea content 54 mgm., and Ambard's index stood at 0.156. The slight fall in phenolsulphonephthalein excretion and rise in blood-urea content would not have attracted much attention, as his clinical condition appeared to be improved, had not his Ambard's coefficient been markedly raised, which aroused the suspicion that despite apparent clinical improvement progressive renal impairment was taking place. This was corroborated by further functional studies a week later, as phenolsulphonephthalein excretion had now fallen

to 40 per cent, blood-urea content had risen to 60 mgm., and Ambard's coefficient to 0.165.

The estimation of the chlorides in the urine was of the greatest value in differentiating the group. On arrival at the base the resolving group were all passing a urine of normal or raised chloride concentration. In the non-resolving group, however, the chloride concentration was very low in half the cases. It would be interesting to know if the concentration was lowered in every case at the beginning of the illness. Judging from the large total amount of salt passed during the period of diuresis, chloride retention must have been of some duration. In the relapsing cases, both in mild and severe forms, the sudden fall in chloride concentration was the most prompt warning of the recrudescence of the malady. The primary rise in chloride concentration certain of these cases just before the marked fall is noteworthy. The explanation of this finding opens up many fascinating theories which will at once suggest themselves to the reader. As a rule a low phenolsulphonephthalein excretion accompanied a low chloride concentration. In the relapsing cases phenolsulphonephthalein and chloride excretion closely simulated one another, both in their quick cessation and in their slow return to normal. This contrasted with the urea concentration in the urine, which did not fall relatively as low as the chloride, and with the onset of diuresis rose quickly to its original level, as if flushed out of the system with the re-establishment of water output. In two of our fatal cases (R. B. and F. G., table 4), however, which showed a mere trace of phenolsulphonephthalein excretion, the urine contained a relatively high chloride concentration until death, although, owing to the small output of urine, the total excretion was very small. In these cases the chloride concentration of the plasma was above the threshold. In the cases of acute infective nephritis we find a relatively good phenolsulphonephthalein excretion, accompanied by a low chloride concentration in the urine, though the plasma concentration was above the threshold; a similar condition existed in the relapse (W., table 3) due to definite microbic condition. Although in one case, W. V. (table 2), and in two fatal

cases, S. J. and J. B. (table 4), a low chloride concentration accompanied a plasma chloride concentration below the threshold, yet in many other cases inability to excrete chlorides was associated with a plasma concentration well above the threshold level. Chloride concentration is a very complex problem, and may depend on many factors not yet clearly understood, nevertheless the chloride concentration of the urine remains a very sensitive index of kidney function. A continued low chloride concentration in the urine is of unfavorable prognostic significance.

It is difficult to evaluate the results given by the addition of salt to the diet. As a rule, those cases which have been shown by other functional tests to have impaired renal function excrete the extra salt badly, responding neither by a markedly increased output of water nor by a raised chloride concentration. On the other hand, the case which showed the lowest Ambard's coefficient (0.071) in the resolving group gave the worst response to this test. On the whole, however, cases with good renal function excrete the additional salt satisfactorily.

These results show that it is not safe to dogmatize from one type of renal functional test alone; but a combination of the tests described above is of the utmost value in forecasting the immediate course of the disease. Time alone will demonstrate their value in ultimate prognosis.

SUMMARY

1. Cases of war nephritis can be divided into two groups: Resolving and non-resolving.
2. The resolving group is characterized by:
 - a. Rapid disappearance of edema accompanied by a distinct diuresis, copious excretion of chlorides, and fall in blood-pressure.
 - b. Rapid diminution in amount of albumin in urine.
 - c. Relatively good renal function.
3. The non-resolving group is characterized by:
 - a. Showing disappearance of edema and delayed diuresis.
 - b. Persistent gross hematuria and persistence of albumin in the urine.

c. Development of permanent retinal changes.

d. Grave impairment of renal function.

4. The acute nephritis following a focus of infection is a distinct entity from war nephritis.

5. Relapses are of frequent occurrence in both types of the disease and are of serious prognostic significance. Functional studies during relapse give many interesting results as regards the different methods of excretion of different substances by the kidney.

6. An acidosis of moderate degree is present. In the resolving group this disappears with general improvement, but in the non-resolving group alkali therapy is required to restore the normal acid-base relationship.

7. Functional tests are of the greatest value in forming an opinion as to the extent of renal impairment. The gravity of certain cases may be entirely overlooked if one depends on clinical observation alone. In the early stages of the disease the excretion of phenolsulphonephthalein, the urea content of the blood, and the concentration of the chlorides in the urine are the most helpful. When the acute symptoms subside and the above tests give more or less normal results, Ambard's coefficient often shows evidence of a damaged kidney.

8. Prognosis as to ultimate complete recovery, even in the resolving group, must be guarded. In the non-resolving group many cases show relatively early in the disease evidence of permanent renal change.

9. The exhibition of alkali therapy is of distinct service in many cases, as shown not only by a restoration of the normal acid-base relationship in the blood, but also by an improvement in renal function.

10. In case dying in the first two weeks of the disease an intracapillary glomerulitis is the most striking histological feature; in cases in which death has occurred in the fifth week there is found, in addition, a proliferation of the cells lining Bowman's capsule, intense edema of the interstitial tissue, small round-celled infiltration and flattening of the epithelium lining the convoluted tubules. Cases in which death has been delayed to

the seventh week of the disease show the proliferated cells of Bowman's capsule replaced by fibrous tissue, with resulting sclerosis of the Malpighian tuft, increase of interstitial tissue, and widespread and severe tubular changes.

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PLATE 1

FIG. 1. Section of kidney from J. G., who died on 13th day of disease, showing two glomeruli exhibiting cellular proliferation. One glomerulus has protruded into the proximal convoluted tubule. $\times 80$.

FIG. 2. Section of kidney from R. B., who died on 34th day of disease. The glomeruli are lobulated. Two show early proliferation of the cells lining Bowman's capsule, while in a third this has progressed farther and a large mass of cells partially fills the capsular space. The tubules are separated by young edematous connective tissue. Some areas are infiltrated with small round cells. The epithelium of the tubules is flattened; some tubules contain casts, others blood or large mononuclear cells. $\times 60$.

FIG. 3. Section of kidney from J. B., who died 45th day of disease. Note the crescentic thickening of Bowman's capsule; one glomerulus is almost obliterated. The tubules are dilated; some contain casts, hyaline and granular; others blood or large mononuclear cells. $\times 50$.

FIG. 4. Higher power view ($\times 180$) of a glomerulus seen in figure 2, showing lobulation of tuft, proliferation and desquamation of cells of Bowman's capsule, and surrounding small round-celled infiltration.

FIG. 5. Higher power view ($\times 180$) of a glomerulus from same kidney as figure 3, showing strangulation of Malpighian tuft and obliteration of capsular space by newly-formed connective tissue which has largely replaced the proliferated cells of Bowman's capsule.

FIG. 6. Section of kidney from C. M., who died on 17th day of disease. In this case war nephritis was complicated by a staphylococcal septicemia. This section shows exudation of blood and leucocytes into the capsular space. In one glomerulus the resulting fibrin formation partially fills up the capsular space and can be seen plugging the proximal convoluted tubule for a considerable distance. The majority of the tubules contain red blood corpuscles and the interstitial tissue is invaded by polymorphonuclear leucocytes. $\times 50$.

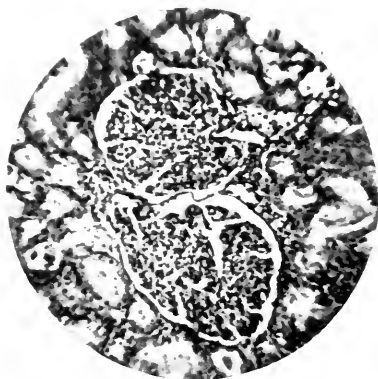


FIG. 1

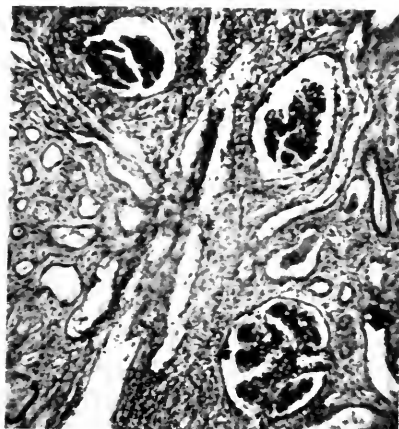


FIG. 2

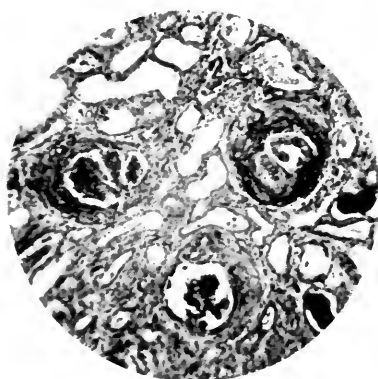


FIG. 3



FIG. 4

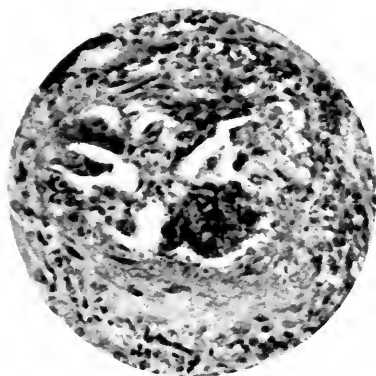


FIG. 5

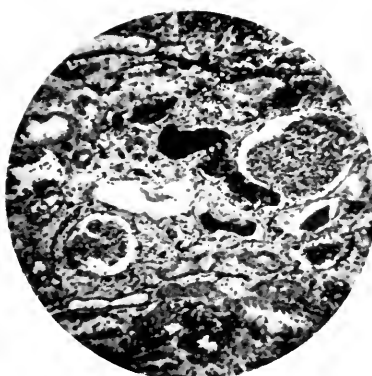


FIG. 6

PLATE 2

FIG. 7. High power drawing from a section of same kidney as figure 1, showing a portion of glomerulus with proliferation of endothelial cells in the glomerular capillaries. The nuclei of one of these cells show mitotic division.

FIG. 8. High power drawing from a section of kidney of J. D., who died on the 31st day of disease. The glomeruli show multiplication of the nuclei lining Bowman's capsule. Just at the mouth of the proximal convoluted tubule of the central glomerulus a collection of proliferated cells is seen. The Malpighian tufts, still enlarged, show marked cellular proliferation and an absence of red blood corpuscles. Lobulation is not marked and there is no invasion by fibrous tissue. The interstitial tissue is very edematous and contains areas of small, round-celled infiltration. The widely separated tubules are dilated, their epithelium is flattened; mitotic figures (marked Δ) are frequent, and their lumen often contains granular debris, mononuclear cells, and red blood corpuscles.



FIG. 7

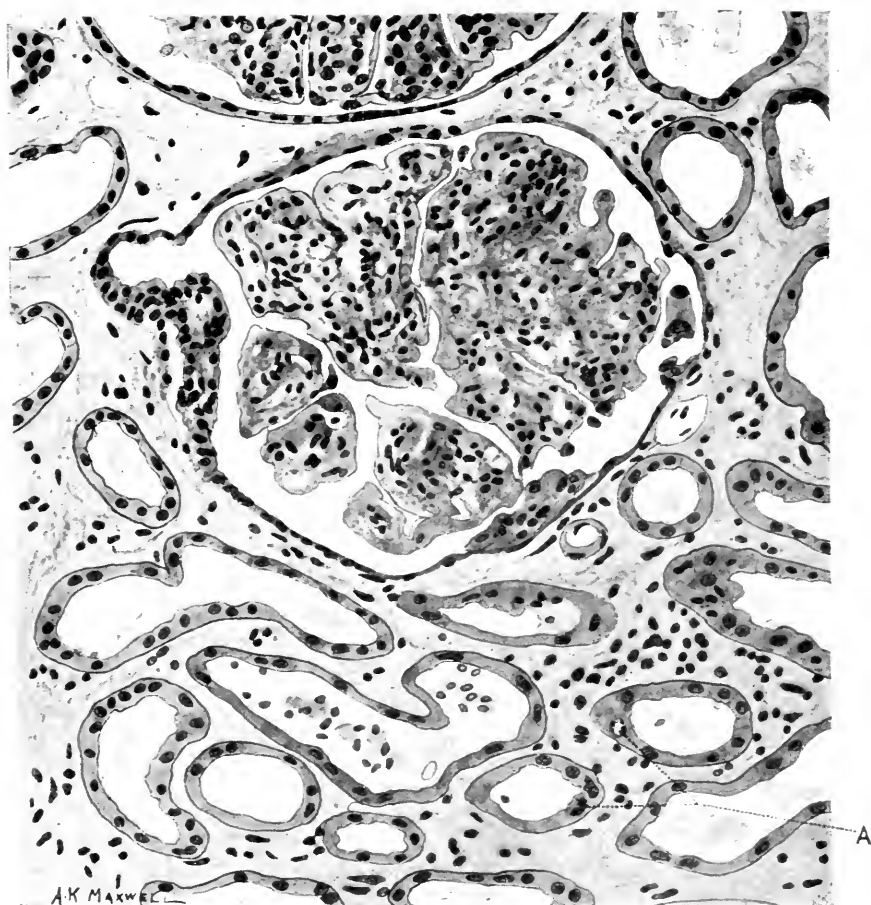


FIG. 8

PLATE 3

FIG. 9. High power drawing from same section as figures 3 and 5, showing proliferation of cells of Bowman's capsule with formation of crescent and its invasion by fibrous tissue. Lobulation and fibrous thickening of Malpighian tuft. Connective tissue can be seen passing into adjoining interstitial substance of kidney, which is increased in amount. Some of the tubules are seen containing casts, hyaline or granular, with nuclear remains; other contains blood or large mononuclear cells. Tubular epithelium is swollen and irregular; sometimes flattened. In one tubule hyaline droplet formation is well seen.

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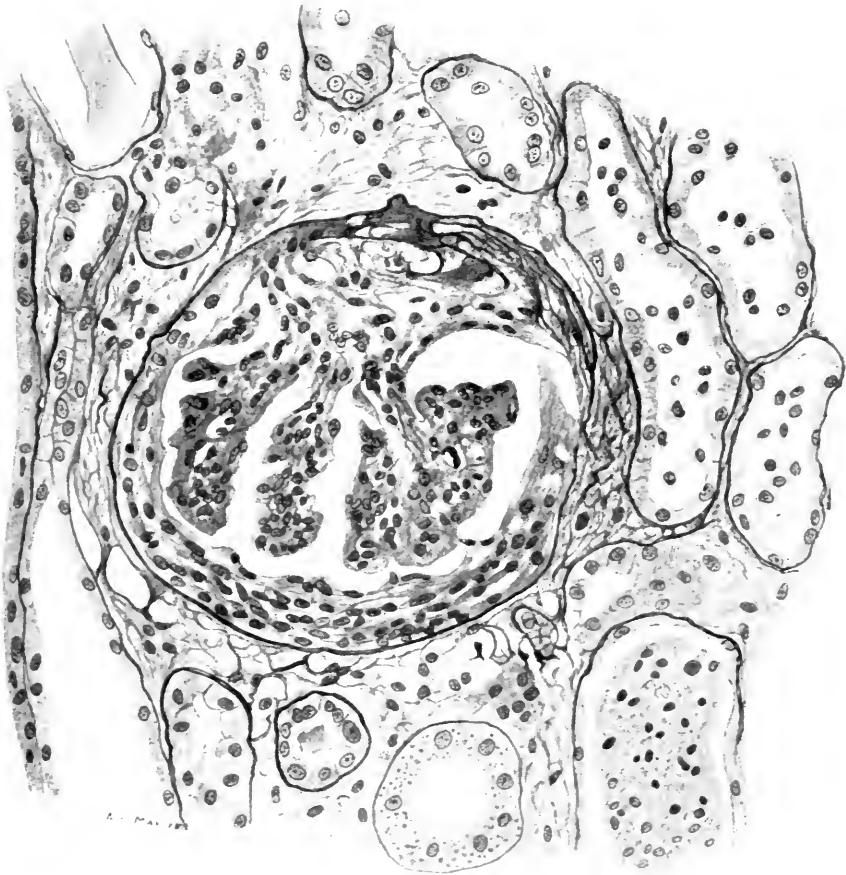


FIG. 9

EXPERIMENTAL HYDRONEPHROSIS—REPAIR FOLLOWING URETERO CYSTONEOSTOMY IN WHITE RATS WITH COMPLETE URETERAL OBSTRUCTION

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The literature relative to experimental hydronephrosis is enormous. Original contributions personally reviewed number more than three hundred which is only a partial list. The problems studied are multiform and the conclusions regarding the experimental results are in turn influenced by the particular problem in mind. Nevertheless, it is surprising to find so much confusion.¹

The mechanics of simple hydronephrosis apparently carry sufficient complexity to defy a clear and thoroughly satisfactory explanation. The differences noted with complete, partial or intermittent obstructions are complicated by the variable changes occurring in the course of any one type of obstruction.²

¹ A complete bibliography of the subject is lacking. Some sort of a systematized classification and general review of the great amount of valuable experimental work reported would be both instructive and interesting. This may be given in a future communication.

² It is surprising how general is the belief that complete ureteral obstruction causes immediate cessation of urinary secretion and is followed by renal atrophy and never by hydronephrosis. As an example, William J. Mayo, at the 1916 session of the American Medical Association in his paper on "Radical Operations for the Cure of Cancer of the Second Half of the Large Intestine Not Including the Rectum" advocates tying the ureter when it cannot be detached and states: "This permanent ureteral obstruction has not been followed by any unfavorable results, and in no case has it been necessary to remove the kidney at a later date because of it." And John W. Draper of New York, in the discussion fully subscribes to the idea. He said "We have done it on animals upward of fifty times and then watched for the result on the occluded kidney, but there is no result. Just as certainly as the negative renal pressure, which is a necessary part of urinary secretion ceases, becomes positive, all secretion stops and you cannot produce hydronephrosis by tying a ligature tight. The only way to produce it is by intermittent partial obstruction. Complete obstruction is safe. Partial

There are degrees between marked hydronephrosis and renal atrophy with the same type and duration of obstruction in a series of the same species and these changes vary with different species. This variability in anatomic changes has led to discordant ideas and misconceptions. Questions of reabsorption, of filtration, of osmosis, of secretion and of excretion have been attacked through experimental hydronephrosis and the results used in explanation of its pathogenesis.³ Problems of blood pressure as related to anatomic structure, particularly with reference to a collateral or capsular circulation, have been given prominence.⁴ The physics of ureteral pressure and secretory

obstruction is not safe." Practically all experimental work gives opposite findings. Lindemann (*Ztschr. f. klin. Med.*, 1898, 34, 299) tabulates the renal changes as follows:

ETIOLOGY	PRIMARY CHANGE	SECONDARY CHANGE	TERTIARY CHANGE
A. Complete obstruction	1. Primary atrophy or 2. Primary hydronephrosis	3. Secondary atrophy or 4. Hydronephrotic atrophy	Hydronephrotic atrophy
B. Progressive stenosis leading to complete obstruction	5. Uronephrosis	6. Secondary hydronephrosis	
C. Periodic obstruction.	7. Intermittent uronephrosis	8. Secondary hydronephrosis	
D. Partial obstruction (stationary)	9. (Primary) stationary uro-nephrosis		

³ The early work on hydronephrosis was mainly concerned with the problem of renal physiology:

Hermann: *Wien akad. Sitzgsb. Mathnaturw.*, 1859, 36, 349. Heidenhain: *Pfluger's Arch.*, 1874, 9. Sokaloff and Luchsinger: *Arch. f. d. ges. Physiol.*, 1881, 26, 464. Cushney: *Jour. Physiol.*, 1902, 27, 431. Pfaundler: *Beitr. Chem. Physiol. u. Path.* 1902, 4, 336. Frey: *Pfluger's Arch.*, 1906, 112, 71. Starling: *Jour. Physiol.*, 1899, 24, 317. Allard: *Arch. f. exper. Path. u. Pharmacol.*, 1907, 57.

⁴ Voorhaeve: *Virch. Arch.*, 1880, 80. Schmiedeberg: *Arch. f. exper. Path. u. Pharmacol.*, 1882, 3, 290. Lindemann: *Ztschr. f. klin. Med.*, 1898, 34, 299. Richards and Plant: *Am. Jour. Physiol.*, 1916-1917, 72, 594. Barney, J. D.

pressure has stimulated most valuable and interesting researches.⁵ Attempts to correlate renal pathology and renal physiology have been made through technical methods of vital staining⁶ or the more modern renal functional tests.⁷

The ability of the hydronephrotic kidney to undergo anatomic repair and functional restoration is a question of great practical importance and one that has never been satisfactorily determined, either clinically or experimentally. Research in this particular problem is relatively insignificant.⁸ It is inseparably bound to all the foregoing fundamental laws of hydronephrosis, as they may be called, and a clear solution can hardly antedate an understanding of these many basic principles. Either of the conditions of hydronephrotic atrophy or the less frequent simple or infantile atrophy may be the starting point. The degree of repair which occurs will naturally be influenced by the type of pathologic condition it must build from and also by the partic-

⁵ Following the lead of Hermann, Heidehain and others, cited above, may be mentioned such interesting contributions as: Gottlieb and Magnus: *Arch. f. exper. Path. u. Pharmacol.*, 1901, 45, 248. Lucas, *Am. Jour. Physiol.*, 1908, 22. Basler: *Arch. f. d. ges. Physiol.*, 1906, 112, 203.

⁶ The vital staining methods are ideal for studying tubular changes and indicate accurately the functional capability of hydronephrotic kidneys. Suzuki: *Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen*, Jena, 1912.

⁷ Keith and Pulford: *Arch. Int. Med.*, 1917, 20, 853, have emphasized our inability to correlate anatomic and functional changes. The frequent observations of remarkable recovery of renal function on the relief of urinary obstruction in cases of prostatism demonstrates clinically the ability of functional restoration but gives no facts relative to coincident anatomic changes.

⁸ A true regeneration of renal parenchyma has long been thought to be impossible. This is supported by studies of repair after toxic injuries, partial excision or stab wounds of the kidneys. Repair following mercuric chlorid, chromic acid, uranium, etc., has been investigated with the general conclusion that epithelial cells show regeneration of new cells, that compensatory hypertrophy of the remaining parenchyma simulates new cell formation, that restoration occurs after slight injury, but that complete new tubules are never formed (Heineke: *Zeigl. Beitr.*, 1909, 45, Oliver: *Jour. Exper. Med.*, 1916, 23, 301). A review of the anatomic and functional repair studies in the literature by Johnson (*Jour. Exper. Med.*, 1918, 28, 197) has appeared since the author's paper was presented. Johnson fails to mention, however, the important work of Donati. Donati (*Gior. d. r. accad. di Med. di Torino*, 1904, Series 4, 10, 597), in four experiments on dogs and nineteen on rabbits, investigated renal repair after ureterocystone-

ular combination of factors which have led to the development of this type.

That kidney subjected to intermittent obstruction over a certain period might be regarded as more capable of recovery than one whose functional activity has been completely excluded for the same time by a complete obstruction. Partial obstructions on the other hand lead to greater pelvic dilatations than do complete obstructions for the same period. But is the hydronephrotic atrophy of partial or intermittent obstruction, by virtue of some renal function having been continuously possible, more capable than that of the same degree produced by complete obstructions? There must be some renal activity even with complete obstruction, otherwise hydronephrosis would not develop, and this may be the crux of the explanation of the infrequent occurrence of simple atrophy, and is intimately related to questions of blood pressure, filtration, osmosis, tubular absorp-

ostomy. In seven of the experiments at the time of the ureteral transplant a portion of the hydronephrotic kidney was resected as a control of the degree of hydronephrosis. In fifteen (two dogs) the hydronephrotic kidney was removed in from 3 to 43 days after ureteral transplant, the period of hydronephrosis being from 12 to 100 days. In the other eight, different operations were performed on the sound kidney, nephrectomy in two dogs with hydronephrosis of 70 and 80 days, repair of 64 and 80 days, was followed by death in 1 and 2½ days, respectively. Nephrectomy in two rabbits (ureters ligated, 25 and 40 days, duration of ureteral transplant, 35 and 15 days) was followed by death in 4 and 3 days. Donati, with ordinary urinary tests and determinations of the lowering of the freezing point, was unable "to demonstrate that zones capable of function because of the presence of unaltered canals may after removal of obstruction regain normal function," nor could he "determine evidence of anatomic repair in the altered parenchyma." Johnson reports seven experiments on male rabbits with a complete left ureteral obstruction of 3, 7, 14, 17, 19, 19 and 21 days, at which time ureterocystoneostomy was done, and in which right nephrectomy was performed, 5, 16, 35, 14, 18, 3 and 21 days later, respectively. The last four rabbits died of renal insufficiency in 9, 3, 4, and 9 days, respectively, after left nephrectomy. In the first three the phenolsulphonephthalein test became normal in 17, 40 and 152 days, respectively, after left nephrectomy. From these experiments Johnson concludes that "kidneys obstructed for two weeks or less may regain their normal function as measured by the phenolsulphonephthalein test. The longer the period obstruction the slower is the rate of recovery." Both the experiments of Donati and Johnston are unfair tests, as they required their hydronephrotic kidneys not only to regain normal function, but to double the work normally done before ureteral ligation.

tion and infection. Apparently simple atrophy rarely if ever occurs in any animal with partial or intermittent obstruction.

The incidence of infection in any period of the process will modify the result and in determining the facts we shall find that it is sufficient cause to exclude all findings with it present. Infection will undoubtedly largely account for the failure of many

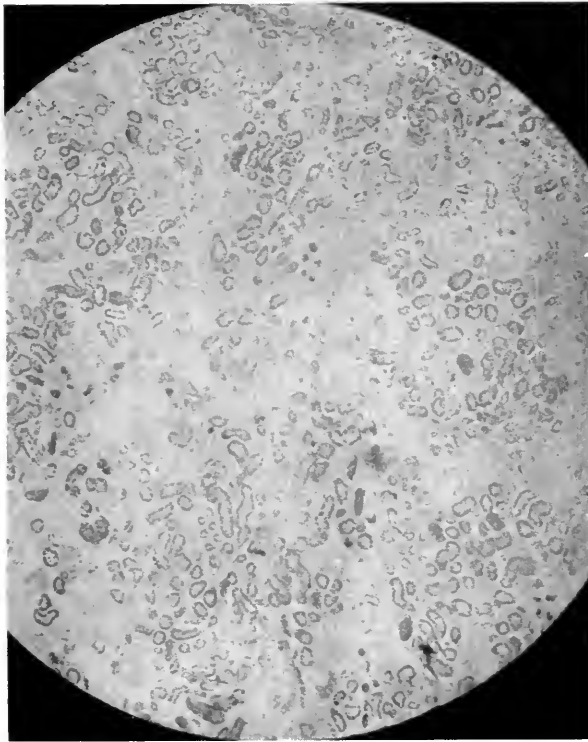


FIG. 1. PHOTOMICROGRAPH (LOW POWER) OF NORMAL KIDNEY OF RAT STAINED INTRA VITAM

investigators to produce hydronephrosis in some instances with complete ureteral obstruction. The infection and not the obstruction causes anuria. Probably infection is more responsible for the occurrence of primary atrophy than the lack of development of the collateral capsular circulation (Lindemann: Barney).

These facts merit a more careful study of the mechanism of hydronephrosis than has as yet been given.

The significance of the compensatory hypertrophy of the opposite kidney has received scant recognition. This anatomic and functional growth is invariable, and I venture the opinion, which I believe will some day be proved experimentally, that a healthy

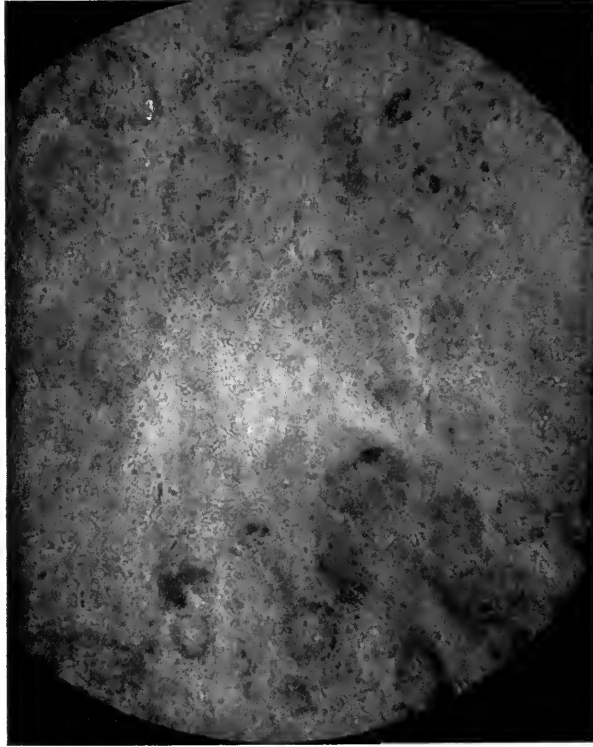


FIG. 2. SAME AS FIGURE 1, HIGH POWER

kidney, once thoroughly accustomed to doing all the work, will, if let alone, continue to do it in spite of any attempt to relieve it of any part of its burden. If this is true, a crippled kidney, though potentially capable of some work, would be completely ignored when brought into competition with its big active and efficient fellow. It would have small chance to improve itself, but

more likely would gradually weaken for want of proper exercise. It will be necessary, therefore, gradually to inhibit the activity of the kidney which has undergone compensatory hypertrophy so as gradually to increase the load on the hydronephrotic side and thus afford a just opportunity for recovery. Complete removal



FIG. 3. PHOTOGRAPH OF MOUNTED SAGITTAL SECTIONS (SERIES I) OF SINGLE HYDRONEPHROSIS FOLLOWING COMPLETE OBSTRUCTION

No. 4, 14 days; No. 5, 21 days; No. 7, 30 days; No. 8, 45 days; No. 9, 95 days, complete ureteral obstruction.

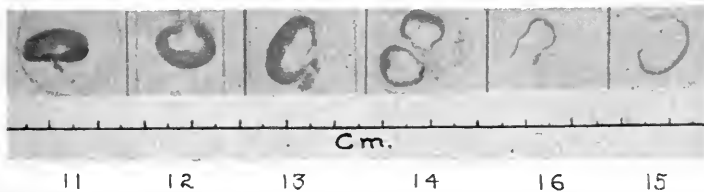


FIG. 4. PHOTOGRAPH OF MOUNTED SAGITTAL SECTIONS (SERIES II) OF SIMPLE HYDRONEPHROSIS

No. 11, 2 days; No. 12, 14 days; No. 13, 21 days; No. 14, 30 days; No. 16, 60 days; and No. 15, 45 days complete ureteral obstruction. Measurements of kidneys No. 11, — $12 \times 8.6 \times 6$; No. 12, — $12 \times 9 \times 6$; No. 13, — $19.6 \times 12.5 \times 12$; No. 14, infection; No. 15, — $16 \times 13 \times 11$, 1 day repair; No 16, — $18.4 \times 15 \times 14$.

of the good kidney is a most unjust test as it at once overwhelms with work an already markedly inefficient organ.

In arriving at a conclusion in regard to the ability of a kidney to repair, we find that one great difficulty in any experimental method is in knowing the degree of pathologic change that exists at the time of relief of the obstruction, whether complete, partial, or intermittent. Any attempt to obtain accurate information on this subject by direct examination of the kidney or of a portion by resection⁹ will handicap that kidney's ability to repair. The indirect method of running a series of control animals has merely a relative value. The anatomic changes in a parallel series of hydronephrosis, owing to the complexity of its mechanism, may be quite dissimilar. Complete obstruction is possible of more accurate control experimentally than are the other types. Repair from hydronephrotic conditions thus produced should form a true analogy for similar conditions of the other types of obstruction.

⁹ Donati, in seven of his twenty-three experiments, removed a cuneiform fragment of the kidney at the time of the ureteral transplantation in order to compare its structure with that found at the end of the repair period.

TABLE OF ILLUSTRATIONS

The comparison of simple hydronephrosis of from 2 to 95 days complete ureteral obstruction with the anatomical and functional changes of repair in hydronephrotic kidneys of similar periods of complete ureteral obstruction that have occurred four to six months after relief of the obstruction

DURATION OF URETERAL OBSTRUCTION	CONTROL, SERIES I, FIGURE 3	CONTROL, SERIES II, FIGURE 4	REPAIR, SERIES III, FIGURES 10-11	DURATION FROM URETERAL TRANSPLANT TO SACRIFICE OF ANIMAL
<i>days</i>				<i>days</i>
2	Fig. 5			
14				
21				
30	Figs. 6, 6-B	Fig. 8 Fig. 9	Figs. 12, 13, 14, 15, 12-A Figs. 16, 16-B.	
45				119
60				165
95	Figs. 7, 7-C			99
120				116
				92

The purpose of this paper is an experimental study of repair after hydronephrosis in white rats. White rats show almost constant findings after complete ureteral obstruction. The gradations of hydronephrosis most beautifully parallel the periods of obstruction and in a large series of experiments we have never seen atrophy occurring in rats without hydronephrosis. Furthermore, rats contract with gratifying rarity post operative urinary

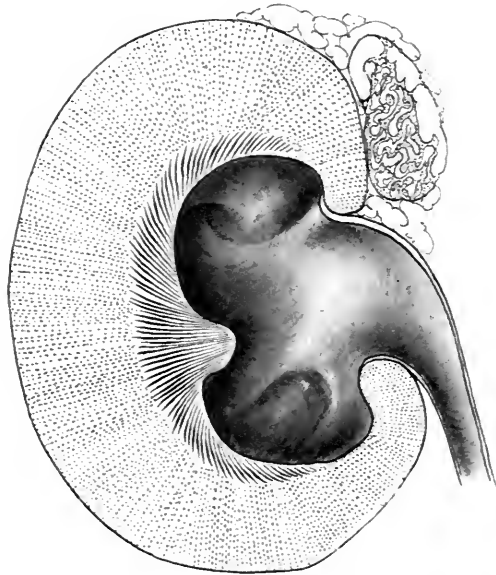


FIG. 5. ENLARGED DRAWING OF KIDNEY OF SECTION 4, 14 DAYS
HYDRONEPHROSIS

Size: $13.4 \times 8.7 \times 8.8$

infection which is so frequent in experimental work on the bladder or kidneys of dogs and cats and the absence of which, we believe, largely accounts for the uniform development of hydronephrosis. Rats are also most suitable for the vital staining methods which have been shown by Suzuki and others⁶ to demonstrate beautifully changes occurring in the tubular system of the kidney with the development of hydronephrosis. This

intravital method of staining furnishes an accurate functional test of renal efficiency. We have in rats, therefore, a method of definite control of the degree of hydronephrosis from which anatomic repair occurs and, in addition to the actual anatomic changes of repair, a relative indication of functional restoration.



FIG. 6. PHOTOMICROGRAPH (LOW POWER) OF SECTION 8, NEAR MID ZONE

Showing tendency of the remaining convoluted tubes to be grouped in small areas near the cortex as protection from the internal hydronephrotic pressure, marked atrophic changes in connecting and collecting tubules and remarkable preservation of glomerular tufts. No convoluted tubules demonstrable by intravital stain, and only an occasional convoluted tubule may be demonstrated by hematoxylin and eosin.

METHOD OF INVESTIGATION

Large white rats were anesthetized with ether. Through a mid-abdominal incision, the bladder was drawn up exposing the ureters on each side. The left ureter was isolated near the bladder and doubly ligated with silk ligatures and divided between them. The animals were then run in two series, one for repair experi-

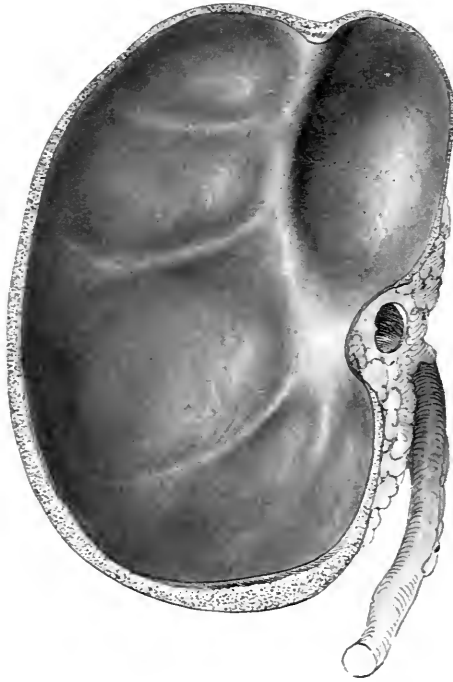


FIG. 6B DRAWING OF KIDNEY OF SECTION S, FIGURE 3; 45 DAYS HYDRONEPHROSIS

Size of kidney: $18.1 \times 14.2 \times 10.3$

ments, the other for a control of the type of hydronephrosis from which this repair would build. In each series before the sacrifice of the animal, intraperitoneal injections of 1 to 2 cc. of diamine blue 1 per cent were repeated every twenty-four hours for from ten to twelve successive injections. Chloroform narcosis was used and through a cannula in the left ventricle or aorta, from

100 to 150 cc. of warm Zenker's fluid were perfused, the right auricle being punctured, thus giving intravital fixation. Specimens were put in the icebox for thirty minutes, then placed in 70 per cent alcohol for two hours, and washed in 80 per cent alcohol for from two to three days and then in absolute alcohol



FIG. 7. PHOTOMICROGRAPH (LOW POWER) OF SECTION 9 AT THICKEST PORTION OF CORTX

No portion of section takes intravital stain. A rare atrophic remnant of convoluted tubules near the cortical surface demonstrable by ordinary histological methods.

(after technic of Evans and Myer). For cutting and mounting sections, the specimens should be put through water very quickly in order to preserve the intravital stain. Other sections were washed to free them of the diamin blue and then restained with hematoxylin and eosin so as to outline other structures than the

convoluted tubules which alone take the vital stain and then only when in a more or less healthy condition.

In the repair series after varying periods of obstruction, the left hydroureter was transplanted under ether into the bladder. This

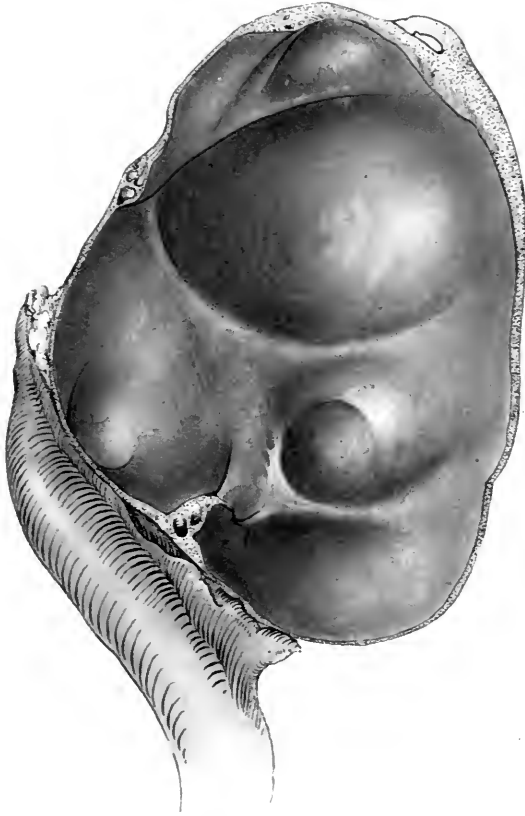


FIG. 7C. DRAWING OF KIDNEY OF SECTION 9, FIGURE 3; 95 DAYS HYDRONEPHROSIS

Size: $20.1 \times 16 \times 14$

at first appeared to be a hopeless undertaking because of the delicate and minute organs involved and an early high operative mortality. Greater experience in anesthetization and protection against shock resulted in a number of successes. The normal ureter of a rat is a fraction of a millimeter in diameter.

but after obstruction becomes several millimeters. The hydro-ureter was carefully dissected along with as much periureteral tissue as possible, since its walls are very thin. The silk ligature, placed at the first operation, was not disturbed. Medium black silk was securely tied over the ureteral end at the site of the old

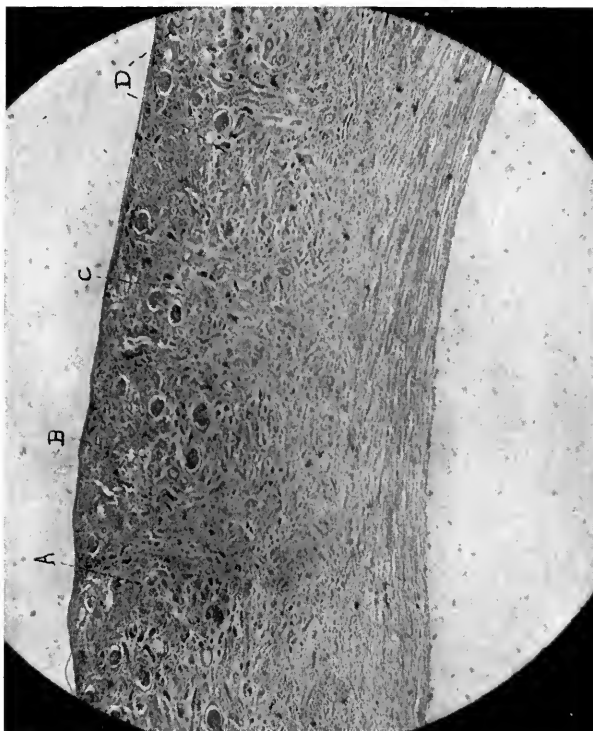


FIG. 8. PHOTOMICROGRAPH OF KIDNEY OF 45 DAYS OBSTRUCTION

No intravital stain. Atrophic remnants of secretory tubules, shown at *A*, *B*, *C* and *D*, grouped largely at right angles to direction of hydronephrotic pressure.

ligature and both ends of this were threaded into an intestinal needle. The bladder was held up and pierced by this needle from the direction of the ureter. The two ends of the silk ligature were brought out on the distal side, and by careful traction on these, the dilated ureter could be pulled clear through both

walls of the bladder in the path previously made by the needle. With very fine interrupted stay sutures (arterial) the ureter was fixed to the bladder walls at the proximal perforation. The sutures were placed through periureteral tissues, care being used not to puncture the ureteral wall with the needle, as it is

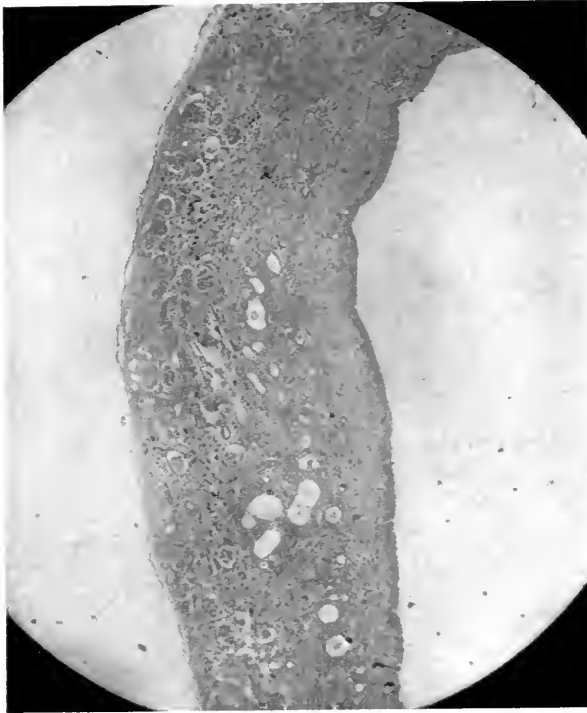


FIG. 9. PHOTOMICROGRAPH OF KIDNEY OF 60 DAYS OBSTRUCTION

No stain intra vitam. Small groups of atrophic convoluted tubules are seen just beneath the capsule. Glomeruli compressed beneath surface, but still well preserved.

too delicate for suturing. The closed end of the ureter is then cut off and traction on the bladder wall allows the open ureteral end to drop back into the bladder. The distal vesical perforation is then closed by one or two fine mattress sutures.

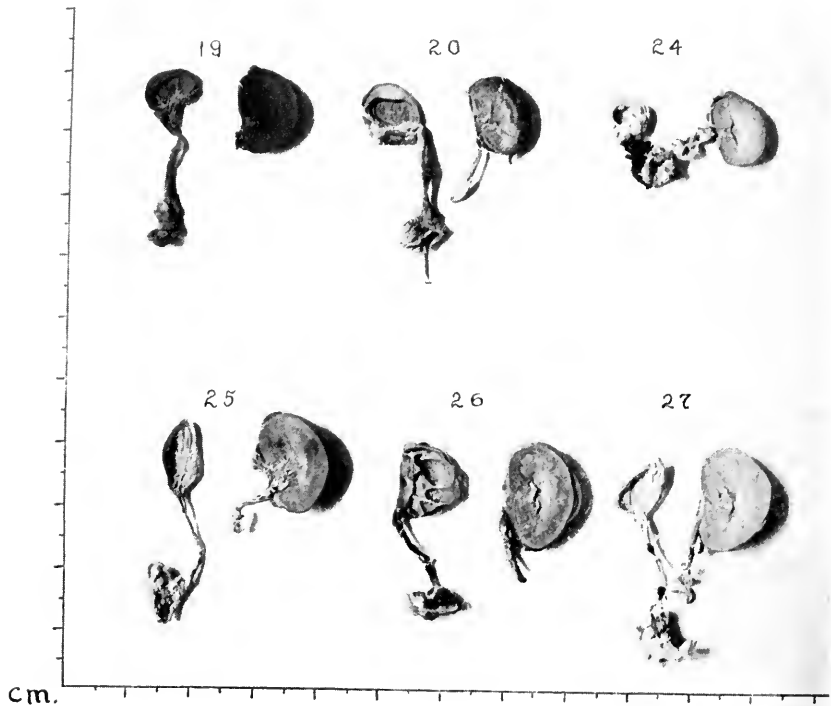


FIG. 10 PHOTOGRAPH OF GROUP OF REPAIR KIDNEYS WITH OPPOSITE HYPERTROPHIC FELLOW

The hydroureter and its site of transplantation into the bladder is shown in each one. The ureteral opening was patent in each one. Pin easily inserted from the bladder as shown in No. 20.

No. 19, 14 days hydronephrosis, 146 days from ureterocystoneostomy to sacrifice of animal. No. 20, 60 days hydronephrosis, 119 days from ureterocystoneostomy to sacrifice of animal. No. 24, 60 days hydronephrosis, 165 days from ureterocystoneostomy to sacrifice of animal. No. 25, 95 days hydronephrosis, 99 days from ureterocystoneostomy to sacrifice of animal. No. 26, 120 days hydronephrosis, 116 days from ureterocystoneostomy to sacrifice of animal. No. 27, 120 days hydronephrosis, 92 days from ureterocystoneostomy to sacrifice of animal.

ANATOMIC AND FUNCTIONAL CHANGES WITH COMPLETE URETERAL OBSTRUCTION IN WHITE RATS

The kidney of a rat under the influence of back pressure from complete occlusion of its ureter undergoes quite definite and uniform gross pathologic changes. It increases in size at first from venous engorgement and edema, but early from the effect of pelvic dilatation. These changes are well shown in the illustrations (figs. 3 and 4). With the increase in pelvic capacity and size of the kidney there is an accompanying thinning out of the renal parenchyma which occurs in a very definite manner. This hydronephrotic atrophy or compression is first seen in the lateral

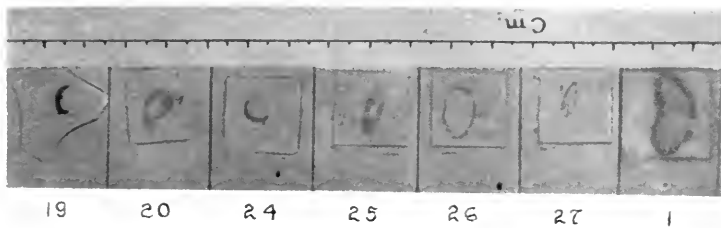


FIG. 11 PHOTOGRAPH OF MOUNTED SAGITTAL SECTIONS OF REPAIR KIDNEYS NOS. 19, 20, 24, 25, 26 AND 27

No. 1 is a sagittal section of normal kidney stained intravitaly, illustrated in figures 1 and 2.

portions of the kidney, and even in three to four weeks has become quite marked so that the lateral walls are very thin. High-grade atrophy next involves the two poles, whereas in the sagittal median portion there is preserved relatively long (sixty days) a ridge of renal parenchyma still resistant to back pressure. (The illustrations are made from sagittal sections and therefore show the best preserved portion of the kidneys.

The changes in the tubular system follow the same order of severity as do the gross changes and are characterized by dilatation, collapse and finally atrophy and necrosis. There is at

first a dilatation of the whole canal system which is least marked with respect to the whole kidney in the median sagittal portion and with respect to the individual radicle, in the proximal convoluted tubules, even Bowman's space being dilated. The collecting tubules are most involved and their dilatation becomes

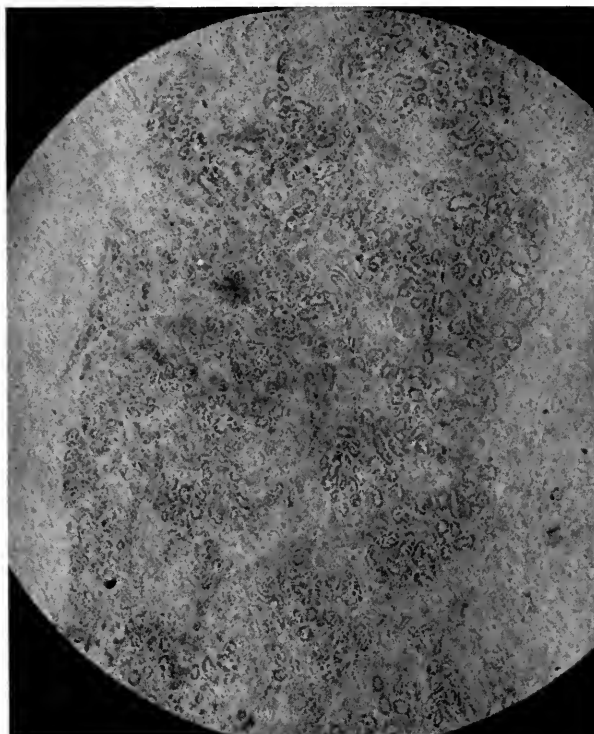


FIG. 12. PHOTOMICROGRAPH (LOW POWER) OF 20B AT MID ZONE, STAINED INTRA VITAM

Shows remarkable regeneration of groups of convoluted tubules. Compare figure 6, a kidney with the same period of ureteral obstruction without repair.

so marked after the first week, in the lateral portions of the kidney, that compression leads to collapse of the less dilated convoluted tubules and Henle's loops above. After the third week the collecting tubular dilatation becomes irregularly marked and is soon confined chiefly to the median portions of the kidney,

collapse having occurred in the other portions. In the lateral portions there is, by this time, universal collapse of the whole tubular system, and an early atrophy of the convoluted tubules is soon followed by disappearance of other tubular structures. This hydronephrotic atrophy is of a high grade, relatively early (third week) in the lateral portions, whereas, in the sagittal median portion the dilated collecting tubules undergo collapse in

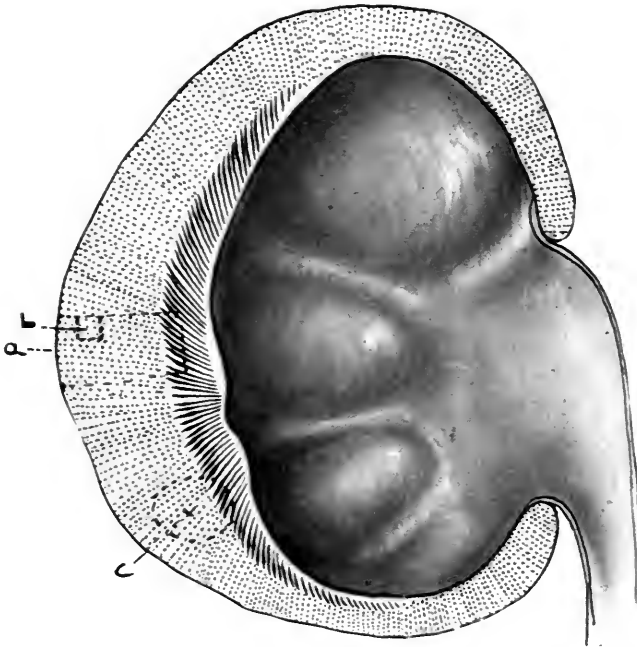


FIG. 12A DRAWING OF KIDNEY OF 60 DAYS HYDRONEPHROSIS, 119 DAYS REPAIR

Size: 9 x 8 x 6

irregular patches, and relatively late (forty-five days) (figs. 6 and 8). Even at sixty days dilated collecting tubules persist and a few atrophic remnants of convoluted tubules may be demonstrated in the median sagittal portion (fig. 9). The rapidity with which atrophy of the cortex occurs, and the uniform order of its development would seem largely dependent upon the course of the tubules in the papillae. Those tubules

opening on the side suffer early a pressure necrosis with atrophy of the corresponding cortical portions. Those opening centrally and having a more or less parallel course to the pelvic axis remain dilated longest and consequently their corresponding cortical portions remain unaffected latest. This explains the irregular

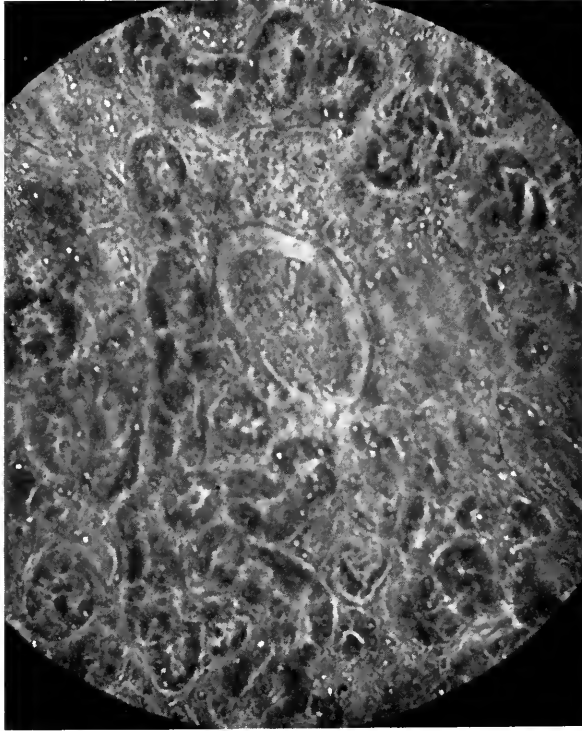


FIG. 13. PHOTOMICROGRAPH (HIGH POWER) OF 20B AT MID ZONE, STAINED INTRA VITAM

Shows remarkable hypertrophy and restoration of convoluted tubules. Compare figure 2 of normal kidney stained similarly.

nodulation in the course of hydronephrotic atrophy. In the rat one linear nodule is the final remnant.

The changes in the glomerular system do not parallel those of the tubular. It is remarkable how long glomerular tufts remain after corresponding tubular structures have completely

disappeared. After forty-five days, however, there is considerable atrophy in the lateral portions, the shrunken tufts being closely massed at the cortical surface (figs. 8 and 9). At ninety-five days this is marked in even the median sagittal portion (fig. 7) and the remaining glomeruli are grouped in clusters. The enumeration of glomeruli in sagittal sections shows a

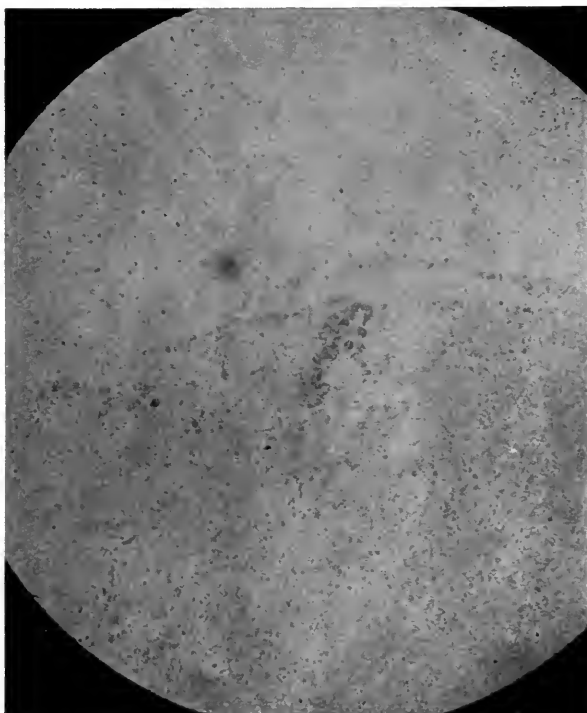


FIG. 14. PHOTOMICROGRAPH (LOW POWER) OF 20B AT LOWER POLE, STAINED INTRA VITAM

Two insignificant and atrophic, but functioning groups of convoluted tubules demonstrated. Compare figure 15.

surprisingly relative preservation even after three months obstruction. The glomeruli counted in sagittal sections of 7 normal rat kidneys averaged 347 and in 7 control kidneys of forty-five to ninety-five days hydronephrosis 310. (In those sections with less than 300 glomeruli—2 cases of 246 and 274—infection was present.)

Functional changes with complete ureteral obstruction

The collapse of the convoluted tubules at about the seventh to ninth day in the lateral portions corresponds to the early functional inefficiency of this portion as indicated by the imperfect stain intra vitam. At two weeks this is quite noticeable. At

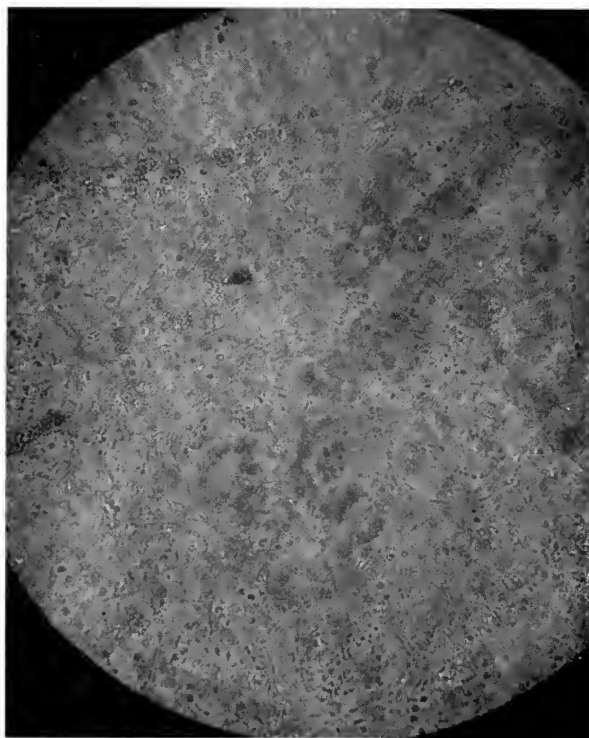


FIG. 15. PHOTOMICROGRAPH (HIGH POWER) OF 20B, IN REGION OF SMALL GROUP OF CONVOLUTED TUBULES VITALLY STAINED, AS SHOWN IN FIGURE 22

There were only four of these small groups in the whole sagittal section of this kidney, in addition to the relatively huge central lobule, figures 20 and 21.

three weeks only the convoluted tubules along the median sagittal portion show intravital stain and at four weeks only poorly stained patches are evident even in this region. At forty-five days the kidneys show no stain whatsoever by intra vitam meth-

ods, although a few atrophic convoluted tubules may be demonstrated by hematoxylin and eosin (figs. 6 and 8) even up to one hundred days (fig. 9).

Anatomic repair. An hydronephrotic kidney, when relieved of back pressure, shows an almost immediate diminution in size



FIG. 16. PHOTOMICROGRAPH (LOW POWER) OF 24C AT CENTRAL REPAIR LOBULE

Quite a respectable number of convoluted tubules apparent. Glomeruli are hypertrophic. Marked connective tissue changes towards pelvic surface; tubular elements massed near cortical surface.

although the general kidney shape is well preserved. This shrinkage is evident in figure 19 and by comparison of the gross specimens and sagittal sections of figures 10 and 11, with those of figures 3 and 4 (see table of illustrations) and of A, B and C, of series I with A, and B of series III. The average size of 5 con-

trol kidneys of thirty to ninety-five days hydronephrosis is: Length, 19.2 mm., breadth, 15.6 mm., thickness, 14 mm., while a corresponding series of hydronephrotic kidneys of thirty to one hundred and twenty days after one hundred and fourteen to one

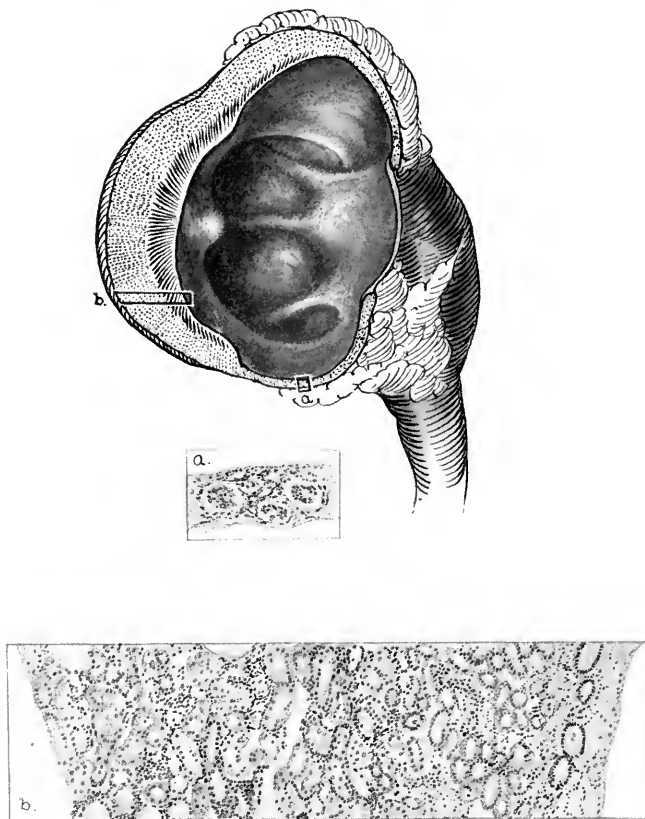


FIG. 16B. DRAWING OF KIDNEY OF 60 DAYS HYDRONEPHROSIS, 165 DAYS REPAIR

Size: $8 \times 6.2 \times 5.2$. Insert A, thin shell of cortex at poles with compressed glomeruli in relatively normal numbers, but with no tubules. Insert B, repair lobule with hypertrophic convoluted tubules.

hundred and seventy days repair averages: Length, 10.3 mm., breadth, 7 mm., thickness, 5.1 mm. (In twenty-four hours after relief from back pressure large hydronephrotic sacs of $20 \times 15 \times 14$ shrank to $13 \times 11 \times 8$.) Another notable gross feature

of the repair kidneys up to sixty days hydronephrosis is the presence of a median sagittal secretory nodule which is beautifully shown in figures 10, 12 and 17. Relief of obstruction after ninety-five, or more, days hydronephrosis results in a considerable, but not relatively so great, shrinkage and there are no renal nodules

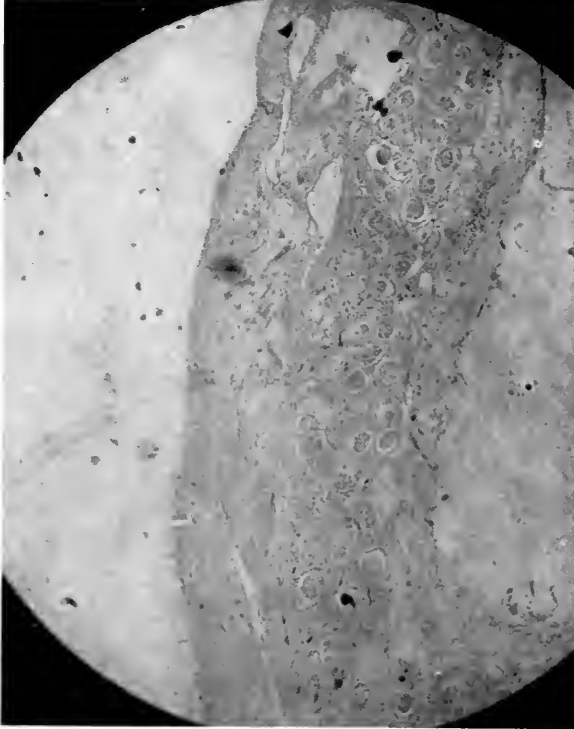


FIG. 17. PHOTOMICROGRAPH OF SECTION 27

Remarkable persistence of glomeruli with almost complete absence of tubular system.

to be seen (fig. 10). The hydroureters also show marked diminution in size (contrary to findings of Rose Bradford in rabbits) but their walls remain thickened.

The collapse and atrophy of the tubules in the lateral portions of the kidney are so extensive by the third week that they are

irreparable and high grade changes in the other portions are beyond a complete restoration to normal. The tubular repair consists in hypertrophy of intact tubules but there is no apparent formation of new tubules (fig. 19). This effort at repair by hypertrophy is well shown by comparing figures 6, 8 and 9 with figures 12 and 17. The structure shown in fig. 6 gives some indication of repair ability but one wonders at the marvelous restoration demonstrated in figures 12 and 17 when he reflects that figure 9 is the control kidney and the analogue from which these repair kidneys had to build. Even figure 6 and figure 8 which are forty-five day hydronephroses instead of sixty, appear hopeless in respect to functional restoration. And yet in figure 12 and figure 17 (both 60 day hydronephrosis) there is present quite a

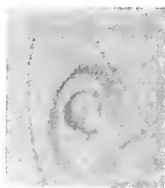


FIG. 18. PHOTOGRAPH OF SAGITTAL SECTIONS OF HYDRONEPHROTIC AND REPAIR KIDNEYS OF 60 DAYS DURATION OF COMPLETE URETERAL OBSTRUCTION SUPERIMPOSED

respectable secretory nodule. The glomeruli related to this nodule likewise show considerable hypertrophy.

Functional repair. The convoluted tubule is the only portion of the secretory radicle which is stained intra vitam, and this is most pronounced in the proximal end. Figures 1 and 2 illustrate a normal rat kidney thus stained. After thirty days hydronephrosis there is shown very little evidence of intravital stain and none whatever after forty-five days. But relief of back pressure in a sixty day hydronephrosis not only restores the ability of convoluted tubular remnants in the median sagittal portion to stain intravitaly but these show even a much more intense stain than normal tubules (figs. 12 and 13). How long such a small patch of tubules, as seen in figures 14 and 15 for

instance, would persist in their connective tissue surroundings is questionable. Probably not long. And the actual functional value of the relatively small nodules of 12 and 13 is likewise questionable. Compared to the huge mass of hypertrophic tubules in its compensatory fellow (fig. 11, no. 1), it is most insignificant. But the interesting fact remains that anatomical repair of no mean degree, both in the recovery and hypertrophy of persisting tubular elements, does occur; and that this repair lobule, as evidenced by staining *intra vitam*, is functionally hyperactive.

CONCLUSIONS

1. Successful hydro-uretero-cysto-neostomy is possible in white rats and permits a study of anatomic and functional repair following removal of a complete ureteral obstruction.

2. White rats are particularly advantageous for experimental work in hydronephrosis. An accurate control of the degree of hydronephrosis produced in complete ureteral obstruction is possible and in consequence the anatomic changes that follow relief of back pressure may be demonstrated. Intravital staining methods may be used with facility and in consequence the functional changes incident to repair may be accurately indicated. Furthermore, infection is relatively infrequent.

3. The anatomic changes that follow complete ureteral obstruction are characterized by an intra and extra pelvic dilatation with an accompanying pressure atrophy of the parenchyma. This compression affects first the sides, then the poles, and the median sagittal portion is relatively resistant. Tubular changes are characterized by dilatation, collapse and atrophy, involving in order of severity first the lateral, then the polar and finally the median sagittal portions. The collecting tubules show the earliest and greatest dilatation and the convoluted tubules dilate the least but undergo collapse and atrophy earliest. In a sixty days hydronephrosis only a few atrophic remnants of convoluted and Henle tubules persist in the median sagittal portion and at ninety days there is none. The glomeruli are surprisingly resistant to the compression and rich clusters of apparently

sturdy glomeruli are grouped at the surface of the thin hydronephrotic rim of three months.

4. Intra vitam stain demonstrates functional insufficiency in the lateral portions of the kidney as early as seven days and is quite noticeable in two weeks. In hydronephrosis of three weeks, intravital staining is largely limited to the median sagittal portion and after one month only poorly stained patches are noticeable even in this region. In hydronephrosis of 45 days or longer no intravital-staining is possible.

5. Infection has a pronounced influence on the type of pathologic changes for the different periods and hastens hydronephrotic atrophy.

6. The effect of relief of back pressure on hydronephrosis of twenty-one to sixty days is shrinking in size with preservation of kidney shape and the grouping of all tubular remnants in one relatively large median sagittal lobule. The tubular and glomerular elements of the central lobule show definite hypertrophic changes. In hydronephrosis of ninety-five days or longer no such central lobule is noticeable.

7. The central lobule developed after relief of obstruction in hydronephrosis up to sixty days shows many hypertrophic convoluted tubules which stain intensely by the intravital method. New formation of tubules cannot be demonstrated. The recovery and hypertrophy of already markedly atrophic structures and their renewed susceptibility and even hypersusceptibility to intravital staining is evidence of the ability of hydronephrotic kidneys up to certain stages (sixty days) to undergo considerable anatomic and functional restoration. In hydronephrosis of ninety-five days or longer recovery, either anatomic or functional, of the secretory elements cannot be demonstrated.

OPERATIVE TREATMENT OF SEMINAL VESICULITIS¹

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During the past few years the value of surgical drainage of the seminal vesicles has become more generally appreciated, due in large measure to the conviction that many disturbances, especially in joints, are due to focal infection from which infectious emboli or toxins gain entrance into the circulation and produce metastatic disturbances in other quite remote structures of the body by some peculiar selective action of the particular infection.

The inter-relationship of gonorrheal infections of the prostate and seminal vesicles to arthritic manifestations is, of course, acknowledged by this medical body and nothing to support this view need be said.

It is a singular pleasure to realize that the conception of metastatic gonorrheal arthritis was first presented by one of our members; but it is to be regretted that we have been so tardy in appreciating what Dr. Fuller had repeatedly pointed out in this connection. It is with a sense of personal apology, in a way, that I take this opportunity to pay tribute to his teachings and to express my appreciation of them. It is not the intention of this paper to trace and explain the cycle of focal infection in the deep genital structures to metastatic manifestations, as such is clear to us all, nor to offer anything but histologic findings from material recovered at operations to prove that infections of the prostate and seminal vesicles usually exist together. It is furthermore unnecessary to point out that chronic infections of these structures may be the sole cause of a permanent urethral discharge. All these facts are understood and acknowledged

¹ Read before American Association of Genito-Urinary Surgeons, Atlantic City, June, 1919.

without question. The object of this paper is to present only *personal clinical and operative* experiences together with results and pathologic findings.

The selection of cases for seminal vesiculotomy should include those which have local or general manifestations dependent upon acute and chronic focal infections in these organs which cannot be overcome by the usual non-operative methods of treatment.

The pathologic classification consists solely of acute to chronic, non-tuberculous, grades of inflammation of the genital tract, beginning with the prostatic urethra and including the structures therein, the prostate, seminal vesicle, vas deferens, and epididymis, with the predominating feature of the inflammation located in the seminal vesicles and prostate. It is the retention of the products of inflammation in the seminal vesicles, and in some degree in the prostate, that results in the clinical symptoms, both local and general.

As infections in the prostate and seminal vesicles produce a somewhat varied clinical picture, they have been divided into four groups for consideration: (1) The inflammatory group, (2) the rheumatic or metastatic arthritic group, (3) the pain group, (4) the neurasthenic group.

1. The inflammatory group. Acute suppuration, occurring most often in the seminal vesicles and prostate in the course of acute urethritis, resulting in a febrile state and presenting locally a swollen, tender prostate and distended, painful seminal vesicles. This condition is generally treated by confinement to bed, local applications and drugs to relieve pain, with the result that after the acute process subsides there persists an urethral discharge from the sub-acute or chronic seminal vesiculitis and prostatitis, which may last for weeks or months, even with appropriate local treatment.

There is a group of patients that has come under my care with acute suppuration of the seminal vesicles, some with and some without abscess formation in the prostate. There have been some with an abscess in the prostate, seminal vesicles, and one epididymis, all true abscesses, from which frank pus has been

evacuated. Many of these patients presented the condition usually treated by local applications, hot rectal douches, rectal suppositories or other forms of sedatives, which, with the subsidence of the acute symptoms, lapse into the common picture of chronic seminal vesiculitis and prostatitis. In this group should be included patients admitted to the hospital with a diagnosis of ischio-rectal abscess, in whom there was no rectal disease, but a recent urethral infection; the true condition being a rupture of the seminal vesicle or prostatic abscess into the ischio-rectal fossa. Some of these cases showed no surface



FIG. 1. HIP JOINT. ACUTE INFECTIOUS ARTHRITIS OF GONORRHEAL ORIGIN

Shows absence of inter-articular cartilage, osseous proliferation along the edges of the acetabulum and some atrophy of the articular surface of the head of the femur.

changes on the buttock but rectal palpation revealed not only a swollen, painful prostate, but a tender indurated mass through the lateral wall of the rectum above the prostate. While some of these cases have revealed an abscess of the prostate which had ruptured into the ischio-rectal fossa, there has occasionally been true suppuration within the seminal vesicles as well. One patient had an abscess of many ounces originating in the right seminal

vesicle, which burrowed upward above the pelvic brim, nothing appearing on the buttock surface, and the prostate at operation showing no abscess formation. The group just mentioned, resembling ischio-rectal abscess in most respects, and being mistaken for such, even in the presence of the history of an urethral infection, and opened and drained in the usual manner of treating ischio-rectal abscesses, have as a sequence, in some instances, a fistulous tract leading to the diseased seminal vesicle, as proved by dissecting it to this structure.



FIG. 2. KNEE JOINT. ACUTE INFECTIOUS ARTHRITIS OF GONORRHEAL ORIGIN

Showing proliferation of synovia resulting in localized lips with a certain amount of osseous proliferation resulting in small spurs at the terminals of the joint surfaces; destruction of cartilage lessening the inter-osseous joint space.

I believe we shall come to realize that many so-called ischio-rectal abscesses are in reality ischio-prostatic or ischio-vesicle abscesses and that we should take advantage of early drainage of suppurative seminal vesiculitis as we do with prostatic sup-

puration. While most of the cases of this group may be cured by appropriate non-operative treatment, there are others which cannot be sufficiently drained through the natural channels which must be subjected to operative drainage of the seminal vesicles and prostate to effect a cure. There are cases of cystitis which can be explained in no other way than by the extension of the inflammation in the seminal vesicles to the bladder wall and mucosa.

2. *Rheumatic group.* Under this heading are included joint, tendon, muscle and bone lesions which may be dependent upon a focal infection. Gonorrheal seminal vesiculitis and prostatitis with metastatic lesions fall into the same class of focal infection as those arising from dental abscesses, tonsillar infections or other poorly drained infective foci, from which other parts of the body become secondarily invaded by emboli or toxins entering the blood stream. In searching for the focus which will explain a so-called rheumatic manifestation much differentiated study may be necessary in some cases; but in the differential diagnosis the condition of the prostate and seminal vesicles should be included.

3. *Pain group.* Under this heading are included those with persistent perineal pain, sometimes accentuated by defecation and often referred to the rectum. It is indefinite in character, but extremely disturbing to the individual, and is often associated with neurasthenic symptoms, painful erection, without sexual stimulus, frequent nocturnal emissions, sometimes painful, and bloody semen. This group usually gives a history of previous urethritis, and in the absence of rectal or bladder disease and the presence of palpable changes in the prostate and seminal vesicles, associated with abnormal elements in the fluid expressed from those organs, the cause of pain may be attributed to disease in these structures. Changes in the verumontanum may be associated with the changes in the prostate and seminal vesicles, and occasionally treatment of this structure alone may relieve the distressing symptoms.

4. *Neurasthenic group.* Under this heading are included those with but slight physical findings of disease in the seminal

vesicles as already enumerated and mental symptoms in the nature of depression, melancholia and apprehension, associated especially with sexual features; the so-called sexual neurasthenia.

My clinical experience with patients falling into these four groups by non-operative and operative treatment not directed to the removal of the focus in the prostate and seminal vesicles has been discouraging.

There have been many cases in the *inflammatory group* which with acute suppuration in the prostate required drainage; but at the time the acute suppuration in the seminal vesicle was neglected and the subsequent condition was that of the usual chronic prostatitis and seminal vesiculitis case. The group of acute cases resembling ischio-rectal abscesses receiving simple incision and drainage frequently had persistent sinuses, some for long periods, and some required repeated operations and prolonged local treatment by massage, etc., and most were not cured.

The *chronic inflammatory group* had some patients who showed little or no improvement, and who vacillated from one doctor to another without resulting cure. The majority of the chronic group was made non-infectious, as far as could be determined, and in most of them the process became quiescent, some with, and some without remissions of symptoms. This latter group is still to be best treated by non-operative procedures, yet it is felt at present that the persistent cases had best be operated upon to remove the focus from which evidence of suppuration arises. In most of these classes the Belfield operation has proved of benefit, yet I believe there are some that cannot be cured by any procedure short of thorough drainage or removal of the seminal vesicles and a prostatotomy.

In the *rheumatic group* non-operative treatment, in the form of fixation, baking, local joint applications, massage, local urethral medication and irrigation, together with vaccines has been of benefit in the milder cases, yet a permanent cure has been rare. The opening and washing of joints added to the usual non-operative treatment has been occasionally beneficial, but on the whole the results have been poor and such treatment as opening the joints has now been discarded.

In the *pain group* and the *neurasthenic group* there has also seemed to me to be a predominating psychological element. Many have had prostatitis and seminal vesiculitis without a positive gonorrheal infection. Often there has been no history of the gonococcus infection nor could the gonococcus be found, but the abnormal amount of prostatic and seminal vesicle secretion persisted, and staphylococci and *B. coli* were not infrequently discovered in the secretions. The symptoms in these two groups may be dependent upon disturbances in the deep genital structures, yet most patients have had a queer mental attitude, especially in connection with sex relations; are often poor physical specimens and without physical employment or pleasures. It has been found that most of them suffered from constipation and other indefinite ailments which may be attributed to lack of physical pursuits and play a part in the general disturbances. This group has improved in my opinion, quite as much from a domineering personality and improved general perspective as from any non-operative or operative procedure, except in those patients where the deep genital structures gave evidence of a real inflammatory condition. In these latter patients, who number small in the group, some have been much improved and some may be considered cured by vesiculotomy or vesiculectomy and prostatotomy. On the whole these two groups have been subjected to operations reluctantly and only as a last resort with little expectancy of a cure in most.

My operative experience includes 194 patients; 52 in the inflammatory group, 128 in the rheumatic group, and 14 in the pain group. I have operated on none with neurasthenic symptoms alone, but most of the 14 patients in the pain group might be called neurasthenics, the only real symptoms being pain in the perineum, rectum or genitals, associated with pathologic findings in the prostate and vesicles, from which it was thought that the neurasthenic symptoms might arise. There has been no mortality.

Results. In the *inflammatory group* there are 52 cases; 17 of them were of the *acute variety*, 5 having suppuration of the prostate as well, and 4, besides showing pus in the seminal vesicles

and prostate, had a unilateral suppurative epididymitis. There were 5 other cases in which rupture of the seminal vesicle or prostatic suppuration had invaded the ischio-rectal fossa. There were 5 cases in which the suppuration was confined to the seminal vesicles.

Fifteen of these 17 cases can be considered cured, and all showed the immediate improvement incident to the evacuation of pus. With the establishment of drainage, pain was relieved, the temperature and leucocytosis dropped, and it remained only to care for the infection in the urethra. The course of these cases following suppuration in the seminal vesicles and prostate leads to the feeling that if such infection of these structures would go on to suppuration whereby all the foci of infection became confluent, a more rapid cure may be expected. Those cases in which the suppuration was in the seminal vesicles alone proved the hardest to cure, as the remaining foci of infection present in the prostate required further treatment, and in 2 patients the prostate continued to give some evidence of chronic infection for long periods.

Thirty-five of the 52 cases in the *inflammatory group* were of the *chronic variety*, having received local treatment over periods of months or years, the process being relatively quiescent at times, to be followed by acute exacerbations without known cause, or from obvious lowering of the local or general resistance. Vaccines which were employed in some of the cases proved of little or no value. The cases forming this group were subjected to operation only after it was evident that the inflammatory lesions could not be drained through the natural channels by the usual methods of non-operative treatment.

There were 6 patients in this group who had sinuses following a rupture of a suppurative seminal vesiculitis or prostatitis, each giving a history of having had an abscess develop during a gonorrhea and present on the buttock, which was incised. In one of these the sinus led to the seminal vesicle on one side, and in the other five it could not be determined that the sinus did not originate from the prostate. Each of these cases, however, had evidence of both seminal-vesiculitis and prostatitis.

Eighteen cases in this group required but little local treatment following operation to effect a cure and all may be considered greatly improved. In many, nearly all suppurative symptoms disappeared before the operative wound was healed and have had no further discharge. Especially is this true of the cases where the infection was chiefly in the seminal vesicles.



FIG. 3. FOOT. ACUTE INFECTIOUS ARTHRITIS OF GONORRHEAL ORIGIN

Showing slight osseous proliferation at metatarsal-phalangeal joints, especially the first; periosteal proliferation and erosion of cartilage in the tarso-phalangeal joints.

In the *rheumatic group* there were 128 cases. Many of these patients had been invalids, periodically, for many years. Some had monarticular affections, while others had multiple joint and tendon affections. Sixteen had so-called spurs of varying types on the under surface of the os calcis or other bones, and when present on the os calcis were bilateral, except in one patient.

Most of the cases had received nearly all known forms of treatment with varying benefit, but none had been cured. Accompanying urethral discharge, either acute or chronic, was the rule; and many who had become relatively free from rheumatic manifestations or apparently cured, were prone to a return of severe rheumatic symptoms most commonly following a new infection.

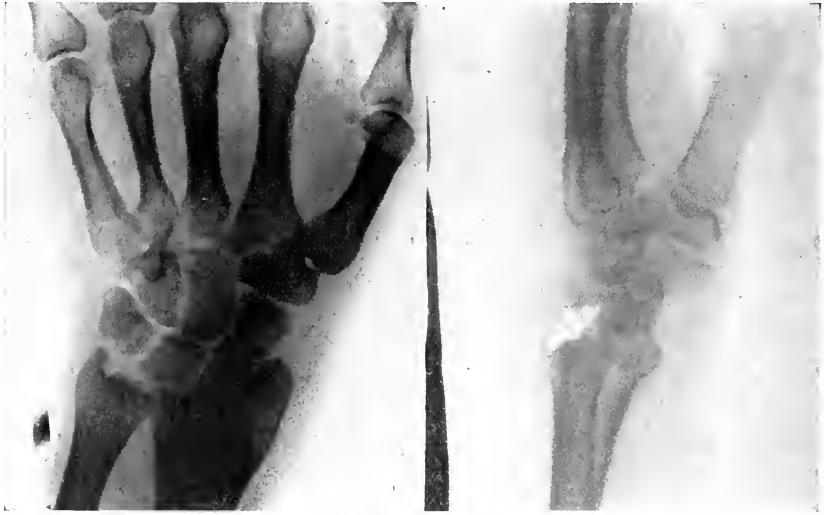


FIG. 4. WRIST JOINT. ACUTE INFECTIOUS ARTHRITIS OF GONORRHEAL ORIGIN

Shows a thinning of cartilage, particularly over the ulna; ulceration of the cartilage over the radius and atrophy of the end of the ulna and small bones adjacent to it.

Removal or drainage of the seminal vesicles and drainage of the prostate in this group has given the most striking results and this procedure has changed what was previously a most hopeless condition into one of the most satisfactory and brilliant surgical triumphs. Pain has disappeared from affected joints, following the ether recovery in most instances, and even large, swollen joints have often become normal in appearance within twenty-four to forty-eight hours following operation. While the explanation of this phenomenon is wanting, the facts remain,

and I believe it is the statements regarding this rapid relief from pain and astonishing subsidence of periarticular, and often the intra-articular swelling, that has been the cause of scepticism and the belief that such statements are over-enthusiastic on the part of those who have made them.

Periarticular swellings disappear much more rapidly than do those that are intra-articular, and when the intra-articular process has been of long standing, resulting in erosion of cartilage and atrophy of bone, considerable periods of time and appropriate accessory treatment are necessary to take care of such defects. With defects as shown in plate 1, where the articular cartilage of the head of the femur and acetabulum are destroyed, and as in plate 2 where the articular surfaces of the knee joint are diseased and associated with hyperplasia of bone, immobilization and subsequent passive motion had to be employed for long periods before repair and permanent improvement could be expected. In such cases, while great immediate improvement in pain and swelling was evident, these and joints with similar lesions approached a normal function only after many weeks and rarely have become absolutely normal joints. Destruction of cartilage with and without atrophy or hyperplasia of the small bones of the foot (plate 3) and wrist (plate 4) have been more satisfactory in their improvement than have the knee and hip joint affections.

When spurs have been present on the os calcis, they have been removed at the time of dealing with the seminal vesicles and prostate. There have been no recurrences of them. Periosteal changes occurring in long bones have not caused trouble and have been left. The few cases which have been observed following the seminal vesicle and prostate operation have shown that there has been no change in them, and I disagree therefore with those who maintain that periosteal changes dependent upon focal infection will disappear subsequent to the removal of the focus (Figs. 5, 6, 7).

Of the 128 cases in the *rheumatic group*, 18 had destructive intra-articular lesions. 16 had periosteal changes, mostly in the form of spurs on the os calcis, bilateral except in one. All

in the former group may be considered greatly improved, and most of them cured, the worst features being slight limitation in joint motion in those with destruction of bone and cartilage and weakness and some swelling in those with a villous arthritis all with periosteal spurs well cured by the removal of the spurs.

Of the 110 patients without destructive intra-articular lesions, all may be considered cured as far as joint manifestations are concerned.

Of the 128 patients, many had almost immediate subsidence of urethral discharge, yet most had the usual non-operative treatment for varying periods before the discharge disappeared. Especially was this true of the cases with active infection of long standing and those with stricture; and in a few, some discharge has remained more or less constantly. Vaccines have been employed more or less in about one-third of the patients, but those who have not received it have fared quite as well.

There are few cases in the *rheumatic group* that have returned with new gonorrheal infection, and but one who had anything resembling rheumatic manifestations in consequence. This patient was one in whom bilateral spurs were removed and who had bilateral flat feet. He had no joint swelling but considerable pain and tenderness about the ankles and in the back during the new active urethral discharge. Another patient of special interest was one who had the seminal vesicles removed but the prostate left untouched. There was much immediate improvement in the joints but there were exacerbations of signs and symptoms of a mild character off and on. One year and a half after the seminal vesiculectomy, I did a partial prostatectomy with a resulting cure, suggesting, at least, the possibility that a lesion of the prostate may be sufficient to produce the joint condition, which fact is borne out by our histologic study, lesions of the seminal vesicles and prostate often being found associated and sometimes being found in the prostate and not in the seminal vesicle tissue.

There is one patient not included in this series who presented such difficulties in the operation, from fibrous infiltration about the seminal vesicles, that they were not exposed or drained, the

prostate only being incised. This patient had been a helpless invalid for years, nearly every joint in the body being involved, so that he was unable to move or even feed himself. Although the seminal vesicles were not drained at operation, there was a temporary improvement, especially in the swellings of the knees and in regard to pain, but he soon relapsed into his former state. This patient died six months after operation.

In the *pain group* there are 14 cases. This group is the most unsatisfactory in regard to the results. The symptoms have been indefinite in character, associated with neurasthenic features, as mentioned under non-operative treatment. All means of alleviating the symptoms were employed before operation. Transitory improvement by different forms of treatment were not encouraging. All of the cases had evidence of chronic seminal vesiculitis or prostatitis. Nine of the fourteen had a discharge, and one had been proved sterile. In this case I had done a bilateral anastomosis of the vas deferens with the rete-testis for sterility three years previous to the operation on the seminal vesicles. In this case, as in all others of this class, there was an unusual amount of fibrous infiltration about the prostate and seminal vesicles, which, I believe, accounted for the pain. Four of the cases may be considered cured, three improved, and seven unimproved. All of the patients who had discharge were relieved of this feature, and all but one was relieved of pain. On the whole, this group of cases has been the most unsatisfactory of all.

The question as to the *comparative results of vesiculotomy and vesiculectomy* is one upon which I can make no statement from personal experience. In my early operations, while no attempt was made to remove the seminal vesicles unopened, the whole posterior wall was removed, the seminal vesicle tissue thoroughly destroyed, and the area swabbed with crude carbolic acid followed by alcohol, which resulted in a complete destruction of the organ, quite as effectually as its total removal. I am convinced, however, from the pathologic study of our tissue that any part of the seminal vesicle may be infected, and that as a general principle, every portion of it should be most thoroughly drained, destroyed or removed.

Regarding the *question of impotency* as a result of vesiculectomy or vesiculotomy, I have yet to see a case, except in the neurasthenic group, and in this series, some have been improved and some have remained the same. There have been several patients who for a few months after operation had had little sex desire and some who have complained that erection was poor at times, but in all the condition was considered psychical rather than physical, and I am convinced that impotency is not to be considered as a complication unless the patient is told that it will be so prior to operation, and possibly not even then.

Resulting *complications* attending the operation are: The opening of the rectum, bladder and peritoneal cavity, post-operative hemorrhage, and epididymitis. I have opened the rectum four times. In each instance it was immediately repaired; in two the repair was permanent. In one, the repair broke down and the fistulous tract was treated as an anal fistula with a satisfactory result. One had a fistula which has healed, opened and healed again, and has remained healed. I have opened the bladder once, which was immediately repaired and remained so, the bladder being drained by an indwelling catheter for several days. In the patient who had the peritoneal cavity opened, nothing was done to repair it and nothing resulted in consequence of it. There have been five cases of post-operative hemorrhage, which was controlled by pressure without opening and packing the wound, but some had a rectal packing made around a tube. There have been several cases of epididymitis, only, however, when the scrotum has not been supported. None of the cases of epididymitis has suppurated and all have been mild in character.

Pathology. The pathologic process as observed at operation, excluding the suppurative invasion of the ischio-rectal fossa, has varied from early inflammatory stages, where the infection is almost entirely confined to the seminal vesicles and prostate, to the late stages of the disease where there is marked chronic inflammatory infiltration of the tissue surrounding these structures, imbedding these organs in a dense mass of scar tissue, obliterating the normal lines of cleavage between the rectum and

the prostate and the base of the bladder, and so rendering the exposure of the seminal vesicles most difficult, and in two cases impossible. In the early stages of the disease, the prostate is



FIG. 5. FOOT. ACUTE INFECTIOUS PERIOSTITIS OF GONORRHEAL ORIGIN

Shows proliferation of the periostium and spur formation on the ventral surface of the os calcis.

found much swollen and boggy from congestion with blood and infiltration with lymph, and the seminal vesicles distended,



FIG. 6. TIBIA. ACUTE INFECTIOUS PERIOSTITIS OF GONORRHEAL ORIGIN

Shows a localized proliferation of periostium and bone formation on right tibia projecting towards the fibula.

fluctuant organs from the retained products of inflammation and secretion. When these structures have harbored infection over a long period of time, the tissues surrounding them, normally soft, are dense with induration and firmly adherent to the thickened walls of the seminal vesicles and rectum, and the prostatic capsule much thickened from infiltration by scar tissue. The organization of this plastic exudate surrounding the seminal vesicles and prostate may produce contraction of the ureter, which passes under the upper portion of the seminal vesicle, and extension of the inflammatory process may invade the bladder wall, producing a basal cystitis or trigonitis.

In many instances the infiltration of the fascial covering of the seminal vesicles was found so intimately bound to them that they could not be exposed; so that the seminal vesicle had to be opened through the thickened fascia. In the majority of instances, however, a total removal of the seminal vesicles has been successfully performed.

In a few instances, the seminal vesicles in an acute stage of inflammation have been freed from surrounding beds of inflammatory tissue, resembling the common condition of an acutely swollen and distended appendix imbedded in inflammatory tissue. It is this active acute process which, I believe, when left to become chronic, forms the group of cases so difficult for vesiculectomy.

The *vas deferens* has almost invariably participated in the inflammatory process, both acute and chronic, being intimately bound to the seminal vesicles, usually considerably enlarged, and with thickened walls and diminished lumen.

The *material contained within the seminal vesicles* has varied much in amount and character. In some the material has been small, in which instances the tubular structure has been observed as wide open, with thickened walls and a content quite fluid and but slightly cloudy. In some of the acute suppurative cases there has been frank pus, but in most, the material has been sero-gelatinous and opaque. In a few instances amala-cious bodies have been found, and in only the acute suppurative type has the gonococcus been found.

For the purpose of *histologic and bacteriologic study*, a considerable amount of tissue has been collected at operation and subjected to various methods of investigation. A more detailed report of this work will form a future communication, written in conjunction with Dr. H. W. Cook, who has been conducting the pathologic study. The method of obtaining the tissue is as follows: In about 40 per cent of the cases only pieces of the seminal vesicles were removed, and in about 60 per cent the entire structure were excised. The prostatic tissue was obtained by splitting the capsule posteriorly over each lateral lobe and removing a generous section from each lateral lobe, and in some instances a considerable portion of one or both lobes. This tissue was immediately cultured and some dropped into Rosenow's culture fluid for bacteriologic study, and cultures taken from the seminal vesicle and prostate when these organs were first opened. The remaining seminal vesicle and prostate tissue was dropped into Zenker's fluid for histologic study.

Bacteriology. Briefly, it may be stated that the bacteriology is negative. Cultures and smears of the material found in the seminal vesicles at the time of operation have shown no growth of the gonococcus or litmus milk, hydrocele and blood agar, Rosenow's media and other culture media and with the exception of the gonococcus, which has been found in smears in some, but not all, of the early suppurative cases no organisms have been found that were not definitely contaminations.

The apparent absence of the gonococcus is not clearly understood, as this organism must be the original one producing the infection. It is generally appreciated that the gonococcus is not a virulent organism, and that its growth on culture medium is difficult, which may, in a measure, offer a sufficient explanation. These observations, in regard to the seminal vesicles, are exactly those in chronic gonorrheal tubes in the female.

Study conducted to find *organisms in the inflamed tissue* of the seminal vesicle and prostate has also proven negative.

Histology. It has been shown repeatedly in our study that pieces of a single seminal vesicle may show normal tissue and acute and chronic inflammation or any one of the conditions

alone; and that prostatic inflammation, in both the acute and chronic stages, has been found associated with inflammation in the seminal vesicle. It is evident from this study that the whole seminal vesicle is not always involved, and that the inflammation is usually confined to areas, which is likewise true of the prostate.

The grades of inflammation have varied, both in the seminal vesicle and prostatic tissue, from the most active acute to chronic types; both extreme types and intermediate grades have existed together in varying degree in each organ, and often together in both the prostatic and seminal vesicle tissue from one patient; and again the prostatic tissue may be little or not at all involved, while the seminal vesicle tissue from the same patient shows different stages of inflammation, and vice versa. In some patients one vesicle has been found infected and the other normal. This is the exception.

While the pathology and clinical evidence have not all been carefully correlated, enough has been done to impress one with the fact that the lesions seem quite insignificant as compared to the general symptoms and manifestations in many of the patients with arthritic disturbances. Especially is this true in view of the absence of organisms, both in culture and tissue, and as yet I have heard no convincing explanation of the almost miraculous subsidence of the symptoms and manifestations following the removal of foci, which, so far as we can determine are free from organisms and for that reason cannot be considered as virulent as the symptoms and manifestations suggest.

Technique of operation. Regarding this feature, nothing need be said in detail here, as the manner of exposing the prostate and seminal vesicle area is perfectly familiar. There are, however, a few features which have been helpful which I desire to mention. The first is the manner of fixing and holding the prostate while exposing the seminal vesicles. This, I think, is best accomplished by a fork tenaculum, and I have found it more convenient than stay sutures or the tractor introduced into the bladder. The second is in regard to the exposure of the seminal vesicles, which I have found most easy of accom-

plishment by dividing the fascia of Denonvilliers along the superior border of the prostate and stripping it back as a whole, over the seminal vesicle area, rather than to excise it over each seminal vesicle. The next is in regard to delivering the seminal vesicle, which can be greatly aided by drawing downward on the vas deferens while one works around and behind the seminal vesicle with abruptly curved scissors. The next feature is in regard to replacing the rectum in its normal position and obliterating the area of operation and controlling any oozing by inserting a rubber tube covered with iodoform gauze, as a long plug, into the rectum as the final step in the operation. This also serves as a means of escape for gas during the period that the bowels are confined.

PLATE 1

SKIN FLAP DISSECTED AND RETRACTED DOWNWARD, EXPOSING BULB OF THE
URETHRA AND THE MEDIAN PERINEAL TENDON

On either side of the median tendon the openings into the ischiorectal fossa are seen. Insert shows outline of skin incision.

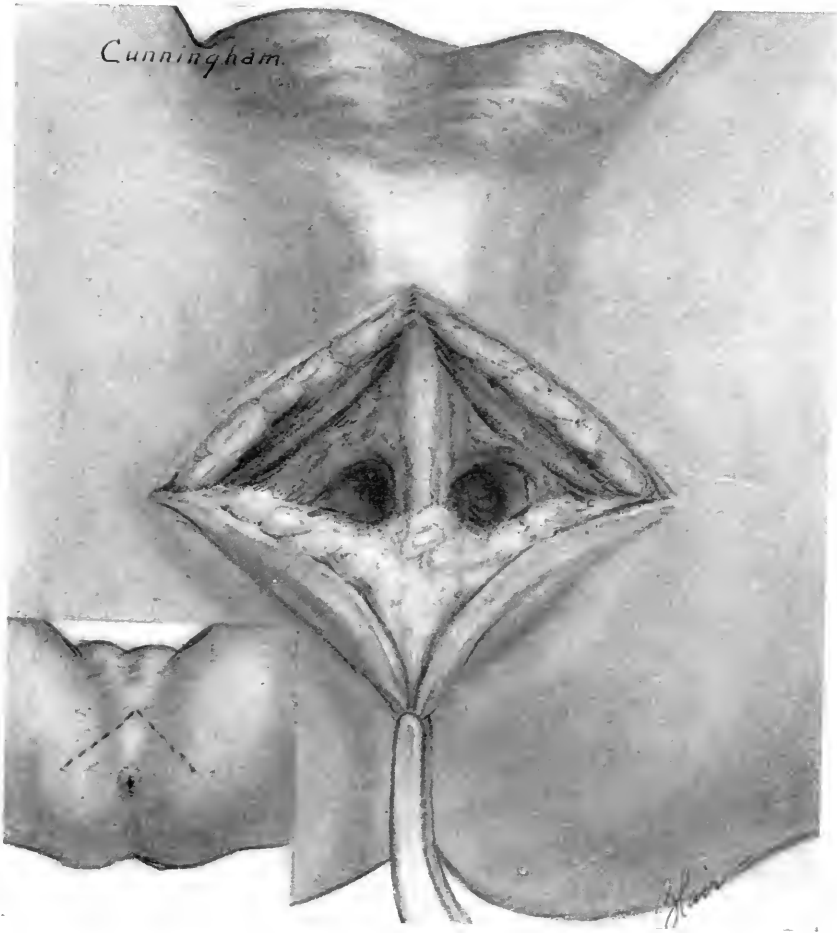


PLATE 2

INDEX AND SECOND FINGERS OF THE LEFT HAND INSERTED INTO THE FOSSAE,
HOLDING THE RECTUM DOWNWARD, WHILE THE MEDIAN TENDON
AND RECTO-URETHRALIS MUSCLE ARE DIVIDED

Dotted line on perineal tendon shows line of incision.



PLATE 3

MEDIAN TENDON AND RECTO-URETHRALIS MUSCLE HELD FORWARD BY FINGER
PRELIMINARY TO THEIR DIVISION



PLATE 4

SPECIAL DOUBLE TENACULUM INSERTED INTO THE PROSTATE JUST IN FRONT
OF THE JUNCTION OF THE PROSTATE WITH THE BLADDER, ELEVATING
THE PROSTATE AND EXPOSING THE SEMINAL VESICLE AREA

One seminal vesicle is seen showing through the fascia of Denonvilliers; and on the other side the fascia divided and retracted, exposing the seminal vesicle. The fascia may be divided along the dotted line, and wiped back exposing both seminal vesicles at the same time. At the bottom of the wound is the special retractor placed over the rectum.

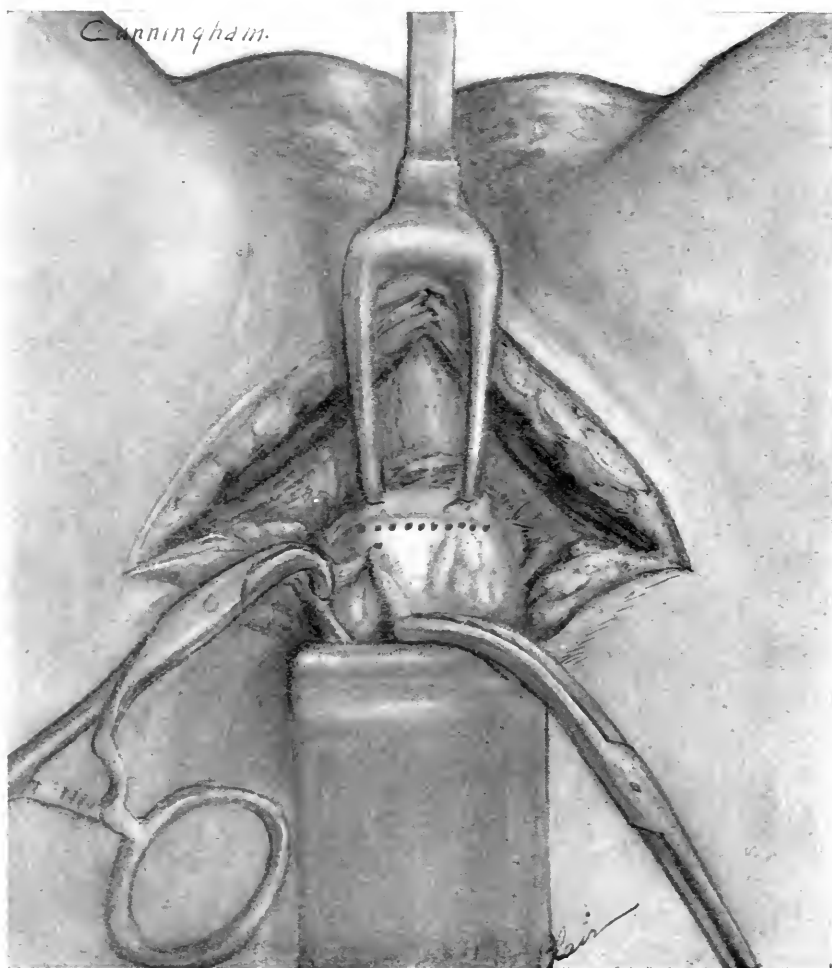


PLATE 5

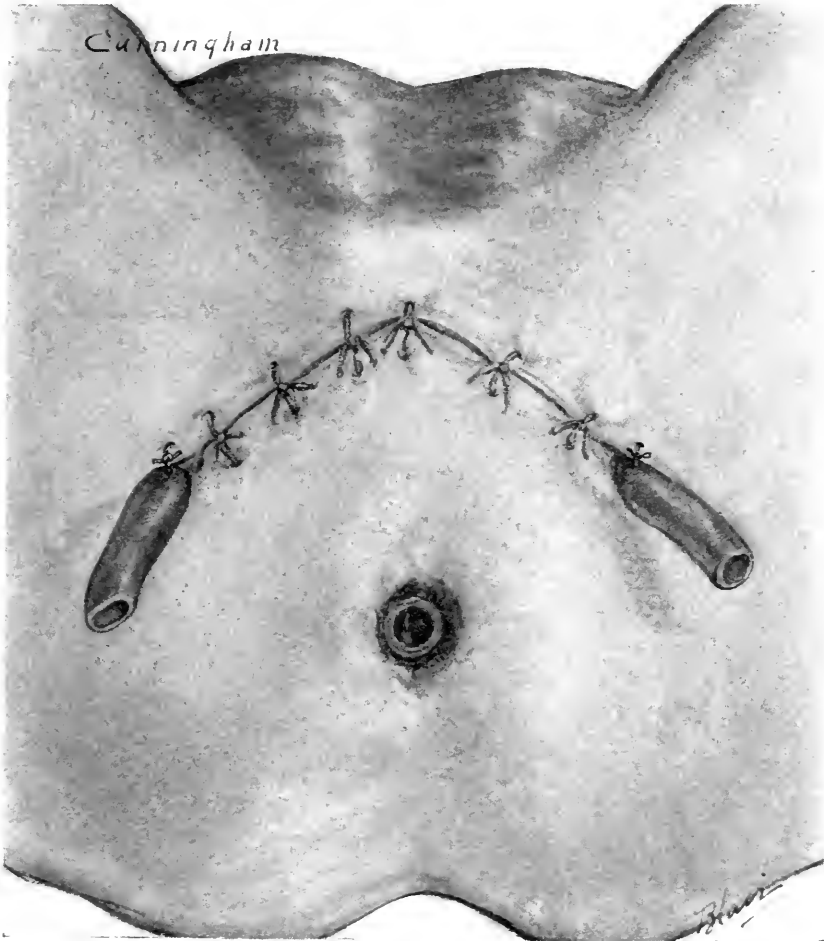
DRAINAGE TUBES CAUGHT IN THE STRUCTURE OF THE SEMINAL VESICLES BY A CATGUT SUTURE AND THE INCISIONS INTO THE PROSTATE TISSUE

Both vasa deferentia are seen between the tubes. Insert shows in detail the opened ducts of the seminal vesicle with sutured tube in position, the opened vas deferens and the retracted fascia of Denonvilliers. If the seminal vesicles are removed the drainage tubes are sutured lightly to the vas at the highest point.



PLATE 6

WOUND CLOSED BY INTERRUPTED SILK WORM GUT SUTURES WITH DRAINAGE
TUBES AT EITHER ANGLE OF THE WOUND, ALSO THE RECTAL
PLUG MADE OF RUBBER TUBING AND GAUZE



THE ETIOLOGY OF VESICAL DIVERTICULUM

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Two types of true vesical diverticulum are recognized in the medical literature. The congenital exists from birth as an anomaly of development. The acquired develops after birth presumably as the result of urinary back pressure. Cavities which communicate with the bladder cavity by intra- or extravescical rupture of its wall, the so-called false diverticula; the rare malformations of multiple or double bladder; a patent urachus which may lead to an hydro-, uro- or pyo-urachus, and vesical hernia, which implies a protrusion of a part of the bladder wall in the tract taken by intestinal hernia, are conditions which should be easily and rigidly excluded.

The clinical differentiation however of congenital and acquired types of diverticulum is most confusing and careful study leads one to believe that the terms are poorly chosen. They have arisen in consideration of supposed differences in etiology, an exact solution of which is wanting. Most writers (Englisch, von Eberts, Fischer, Brongersma, Judd) accept the dual classification and believe in a double etiology. But some authorities (Lower, Lerche, Wagner, Serralach) incline to the belief that all diverticula are acquired, while others (Cabot, Israel, Hofmohl) are as firmly convinced that the great majority have a purely congenital origin. A few men (Young, Kelly and Burnham, Cholzoff, Sigimura) prefer to regard both congenital and acquired factors as active in the production of all types. It has been the general custom to report as congenital all diverticula with muscular walls in which definite obstruction is absent, and as acquired the thin mucous membrane sacs associated with recognizable obstruction. Often a well-marked prostatism has been regarded as merely coincidental when the sacs were large

and muscular. Such a basis of differentiation, in my opinion, is ill-founded, leads to confusion and should be discarded.

The numerous conflicting arguments concerning the etiology of diverticula may be briefly summarized.

1. Reasons presented for the conception of a congenital origin: Diverticula occur as large thick walled sacs unassociated with any evident condition of urinary obstruction, particularly in women and children.

Thick walls similar in structure to the bladder refute the idea of a herniation due to back pressure and furthermore rarely occur in association with prostatic hyperplasia which is then merely coincidental. The diverticula commonly found with hyperplasia are relatively small with thin walls and they are multiple.

The inclusion of an ureteral orifice in the wall of a sac is evidence of congenital malformation, and, again,

No experimental evidence of the occurrence of diverticula under conditions of back pressure has ever been presented.

2. Reasons presented for the conception of an acquired origin: Diverticula are rarely found in the young or in women but occur commonly in men over fifty, at or beyond the age when obstructions are most manifest.

Other evidences of back pressure such as trabeculation or hydroureters, etc., are almost universally present.

The absolute exclusion of obstruction to urination, in some form at some time in all supposedly congenital cases, is not possible.

A study of all cases (frequently not sufficiently detailed to permit analysis) reported within the last twenty years, particularly with reference to age, sex, duration of symptoms, location of the orifice, size and structure of the diverticulum, presence or absence of conditions of obstruction and frequency of associated evidence of obstruction will serve as the foundation for an opinion which is further enhanced by an experience in the study and treatment of 21 personal cases.¹

¹ These cases are reported in detail elsewhere, Vesical Diverticulum, a Clinical Analysis of 21 Cases, Surg. Gynec. & Obst., 1919, xxix, 150-172.

ANALYSIS OF TWO HUNDRED AND FIVE CASE REPORTS FROM 1899
TO 1919

The findings in the various cases reported in the literature are partly summarized in tables 1 to 8. The essentially important points are discussed more in detail in the following paragraphs.

Age. There were only 18 under thirty in 154 cases in which the age is given (see tables 1 and 8). In two of these (Wallfield) the reports are so incomplete as to render them very doubtful. Another case (Young, age seventeen) is probably an hydrourachus. Therefore, less than 10 per cent of the cases occurred in individuals under thirty. Only 7 cases or 4.5 per cent were under twenty and just one case which had a small pouch (Handl) under ten. This sufficiently emphasizes the rarity of the condition in the young. About one-third of all cases occur in the ten years between fifty and sixty.

The incidence above thirty is as follows:

<i>Ages</i>	<i>Cases</i>
30 to 39.....	22
40 to 49.....	23
50 to 59.....	44
60 to 69.....	27
70 to 79.....	18
Over 80.....	2

Sex. Only 10 of 205 cases reviewed (table 2) occurred in women. One of these is a probable hydrourachus (Todd); one so small as to be better considered a deep cellule (Kelly); another (Chaput) is questionable inasmuch as the orifice was neither seen at cystoscopy nor found at operation, and was probably a cyst of the cervix uteri. Therefore, during a period of twenty years less than 5 per cent of vesical diverticula have occurred in women. In two cases (Franck, and Kelly and Burnam) the diverticulum was small and contained stones. Bierhoff's case was a tabetic, Lower's case had an urethral caruncle and both were regarded by the authors as acquired types. The remaining cases give prolonged histories of frequency and had marked trabeculation and cellule formation in addition to the diverticula which were all relatively small.

TABLE 1

Eighteen cases under thirty years of age reported 1899 to 1919 (154 cases)

AGE	AUTHOR	SEX	ONSET SYMPTOM	DURATION <i>years</i>	CONDITION OF OBSTRUCTION	LOCATION OF ORIFICE	SIZE	REMARKS
<i>years</i> $\frac{1}{2}$	Wallfield	Male						Report incomplete—considered an anomaly
3 $\frac{1}{2}$	Handl	Male	Difficulty	$\frac{3}{4}$	False passage in posterior urethra	Right ureter in diverticulum	Small egg, Wall 1 mm.	Autopsy: Bladder wall markedly hypertrophied Loose fold of mucous membrane found hanging from upper wall of bladder producing obstruction
9	Wallfield	Male	Pain and retention		No diverticulum seen			Operation: Intravesical suction method
10	Young, H. H.	Male	Frequency, pyuria	8	Median bar, vesical calculus	Just external to left ureter	Bird's egg	Both ureters dilated, kidneys hydronephrotic, death in uremia
12	Brongersma	Male	Incontinence	3		Near right ureter on posterior wall behind ligamentum interuretericum	Large	
17	Young, H. H.	Male	Pain in left abdomen	3		None seen		Sac on anterior wall presumably a hydroureter
17	Koller	Male	Difficulty and pain	4	Stricture of meatus	Above right ureter	Apple	Bladder markedly trabeculated
18	Marion	Male				Near right ureter		Diverticulum resected and ureter transplanted
18	Howard	Female	Cystitis with incontinence	Since childhood	Vesical calculus	Near right ureter		No evidence of diverticulum in cystogram, death following inversion method of Young

18	Judd	Male	Difficulty	Since childhood	Elongated posterior urethra	Left ureter in diverticulum	No details reported
21	Berry						
22	Young, H. H.	Male			Urethral stricture, posterior urethral valve	4 cm. above left ureter	Left ureter dilated. Bladder greatly trabeculated and thickened
23	Schussler	Male	Difficulty and pain in bladder	1	Contracture of vesical neck	Inside and behind left ureter	Bladder trabeculated. Excision—3 stones found three months after. Lithotomy—urethral dilations—improved
23	Cabot	Male		2		One near each ureter	Excision
26	Chalzoff	Male	Difficulty	6		Left ureter in diverticulum	Bladder markedly trabeculated. Resection. Left ureter transplanted—persistent perineal fistula
28	Kroiss	Male	Suprapubic pain			To left of left ureter	Extraperitoneal excision
28	Ghezzi	Male	Frequency and pain	3		Near right ureter	Death following cystotomy
28	Cabot	Male	Pyuria	2		On right posterior and lateral wall	Excision
29	Cabot	Male		1½		On posterior wall	Excision

TABLE 2
Twelve cases in female reported 1899 to 1919 (205 cases)

YEAR	AUTHOR	AGE <i>years</i>	SYMPTOMS	DURATION	LOCATION OF ORIFICE	SIZE	CONDITION OF CONSTRUCTION	EVIDENCE OF BACK PRESSURE	REMARKS
1898	Kelly	?			Posterior to right ureteral orifice	1 cm. in depth		Bladder trabeculated and numerous cellules	So small as to be better considered as a deep cellule
1899	Huldshiner	?							No detailed report obtainable, regarded by Huldshiner as acquired type secondary to puerperal sepsis
1901	Bierhoff	56			Three in posterior wall	Small	Tabetic	Bladder markedly trabeculated	Bierhoff considered the diverticula as acquired
1906	Chaput	50	Pain in abdomen and difficulty	5 months					Orifice or communication of sac near bladder was never seen on cystoscopy nor found by probing at time of operation
1910	Todd	33	Pyuria	4 years	At apex with patent urachus	Large			Suprapubic excision of "hydrourachus"
1910	Franck	50					Large stone in diverticulum		Dilated orifice and removed stone suprapubically

1914	Kelly and Burnam	47			On posterior wall	2.5 cm. in depth	Small pocket filled with small stones		
1915	Lower	74	Frequency and pain on urination	Many years	Above right ureter		Caruncle at meatus for many years		Lower considers the diverticulum as acquired because of difficulty and frequency consequent to caruncle
1918	Howard	18	Cystitis with incontinence	Since childhood	Near right ureter		Vesical calculus	Bladder trabeculated	Not shown in cystogram. Two operations; first, cystotomy; second, intravesical inversion—death
1918	Howard	36	Frequency and burning	12 years	Above right ureter				No cystogram or operation
1919	Author's case	40	Frequency and burning	20 years	Above and to inner side of left ureter			Bladder trabeculated	Shown in cystogram—no operation
1919	Author's case	56	Frequency and pain	20 years	Four black orifices, one each near ureters and two at base	All small		Bladder markedly trabeculated and many celluloses posteriorly	No cystogram or operation

Initial Symptom. Difficulty or frequency of urination or both are mentioned as the onset symptom in 114 or in 75 per cent of 152 cases. Hematuria is mentioned as the first symptom in 13 cases, cystitis or pyuria in 6, acute retention in 6, pain and burning in 4, pain in the abdomen and pain in the bladder in 3 each, and pain in the lumbar region and chills and fever once each.

These initial symptoms conform in frequency and character to those of any large series of prostatism.

Duration of symptoms. The duration of symptoms varies from a few months to several years. In 96 cases in which it is mentioned it was

	<i>Cases</i>
Less than 1 year.....	10
From 1 to 4 years.....	28
From 5 to 9 years.....	19
From 10 to 20 years.....	16
Over 20 years.....	14
Since childhood or infancy.....	9

Therefore, over 60 per cent had had symptoms for more than five years.

Location of the orifice. The location of the orifice² is mentioned in 163 cases (table 3). There was a single diverticulum in 135 and multiple diverticula in 28 cases. The orifice was found in the neighborhood of one or the other ureteral meatus in 98 of the 135 single diverticula and near both in 25 of the 28 multiple diverticula. The largest number mentioned in any one case is 7 and undoubtedly many of these were large cellules. In a few cases numerous orifices are located in the base. One or the other ureter opened into a diverticulum in 12 cases, and in one case both ureters were thus placed. An analysis of these 12 cases is given in table 4, a study of which will test the weight of the argument that such diverticula are congenital in origin. The writers recognized small prostatic enlargements in 3, and definite contractures of the vesical neck in 3 cases. Handl's case had a false passage in the posterior urethra. There was

² Considerable misinterpretation can arise in locating an orifice by cystoscopy alone, as the author has learned by experience, and as shown by errors cited by Berry, Cabot and Judd.

bladder trabeculation and hypertrophy of its walls in all the other cases.

Size and structure of the diverticulum. The size of the single diverticulum is given in 39 cases, and of multiple diverticula in

TABLE 3
Location of orifice of diverticulum

POSITION OF ORIFICE	SINGLE DIVERTICULUM		MULTIPLE DIVERTICULA			
	Number of cases		Right		Left	
	Right	Left	Number	Cases	Number	Cases
Near ureteral meatus.....	12	11	11	H-J-K-L- M-N-O- R-S-T- V	11	F-H-J-K- L-M-O- R-S-T- T
Above meatus.....	31	19	6	C-D-I-P- Q-Q	6	A-B-B-C- D-I
Above and external to meatus.....	6	8	2	A-G	3	E-G-V
Above and internal to meatus.....	1					
Below meatus (anterior).....	2	1	1	P	1	V
Ureter in diverticulum.....	2	6	2	F-W	3	B-N-W
In fundus or base.....	2	2	2	B-U	2	B-U
On lateral wall.....	4	2				
Total.....	109		50			
In "fundus".....	19		3 A-B-T			
Above ligamentum interuretericum.....	2		1 E			
On anterior wall.....	1		1 U			
In "vertex" "apex" or "dome".....	5		2 B-G			
Total number of cases.....	136		23 (A to W inclusive)			

15 cases. A study of these cases shows that in the 34 cases of single sacculation reported as large (by measurement or designation) 18, or more than half, had definite conditions of obstruction recognized and reported by the observer and in all but 2 cases the bladder wall is mentioned as thickened and trabeculated. None of the large diverticula was in women.

TABLE 4

Cases reported (1899 to 1919) with ureter opening into diverticulum

AUTHOR	AGE* <i>years</i>	INITIAL SYMPTOM	DURATION <i>years</i>	LOCATION OF ORIFICE	SIZE OF DIVER- TICULUM	CONDITION OF OB- STRUCTION	EVIDENCE OF BACK PRESSURE	REMARKS
Marion, G.	56			Seven orifices seen, one swallowed left ureter, others were deep cel- lules, 2 above left. 3 on posterior wall at sum- mit, and one at left of right ureter	2 x 3 cm.		Bladder wall hypertro- phied	Autopsy study: Considered as true congenital diverticula
Young, H. H.	30	Difficulty and fre- quency— used cath- eter six months	11	Right ureter in diverti- culum—sec- ond orifice near left	1, Medium 2, Small	Fibrous pros- tatic ob- struction. Stricture of membranous urethra	Trabeculation	"Poor result" fol- lowing excision of large divertic- ulum, but Bottini operation later gave "excellent" result
Young, H. H.	63	Frequency	10	Left ureter in diverticulum		Right and left lateral pros- tatic hyper- plasia		Suprapubic prosta- tectomy four years ago. Re- moval of diver- ticulum by suc- tion method. Small prostatic nodule removed

Pagenstecher	33	Pain in bladder	1	Left ureter in diverticulum	Small egg	False passage in posterior urethra	Bladder wall markedly hypertrophied	Autopsy study and considered by Pagenstecher as false diverticulum
Handl, A.	3½	Fell off stool upon but-toek—followed soon by difficulty—catheterized four days	3	Right ureter in diverticulum				Autopsy: Diverticulum sac wall was 1 mm. thick, with mucosa, muscle bundles and serosa
Berry, J.	21	Difficulty	Since infancy	Cystoscopically, orifice was "High on anterior surface of bladder at left" but found at operation to be at left posteriorly with left ureter opening into it		Bladder capacity 1500 cc. Residual—510 cc.	Left ureter dilated	Absence of muscle bundles in region of diverticulum where ureter opened into it, treated by excision with Young flap. Reported cured but last note showed 120 cc. residual
Cholzoff, B.	26	Difficulty	6	Left ureter in diverticulum	"Large"		Bladder trabeculated	Resection, ureter transplanted still has perineal fistula

AUTHOR	AGE* <i>years</i>	INITIAL SYMPTOM	DURATION <i>years</i>	LOCATION OF ORIFICE	SIZE OF DIVER- TICULUM	CONDITION OF OB- STRUCTION	EVIDENCE OF BACK PRESSURE	REMARKS
Chute, A.	59			Right ureter in divertic- ulum	"Large"	Small hyper- plasia of prostate	Trabeculation	Perineal prosta- tectomy 1908— 240 cc. residual— orifice enlarged 1910—improved Excision, trans- planted ureter. Three weeks later did Young punch —cure. (used rubber bag to dis- tend sac) Excision of two diverticula
Lerche, W.	38			Left ureter in diverticulum		Contracture of vesical neck	Trabeculation	
Cabot, H.	38	Frequency and pain	13	Left ureter in diverticulum another in region of right ureter	1, 4 cm. in di- ameter 2, 10 cm. in di- ameter	None found	Both ureters dilated. Bladder thick and trabeculated	
Knauf	37	Suprapubic pain	2	Left ureter in diverticulum at left. Right ureter in divertic- ulum at right	1, apple 2, peach	Bilateral pyo- nephrosis and hydro- ureters	Bladder wall very thick— over 1 cm.	Cystotomy—death Over 1000 cc. re- sidual

Personal case	37	Difficulty	5	Left ureter in diverticulum 3 diverticula near right	1, 11 x 10 x 13 2, 3, 4, 10 x 7 x 9	Contracture of vesical neck	Both ureters dilated. Trabeculation	Extraperitoneal resection of 4 sacs. Young's flap operation on left ureter. Right ureter transplanted—2 punch operations subsequently
Personal case	67	Frequency and difficulty	Many years	Left ureter in diverticulum 1 above right ureter, 2 in base	1, 5 x 4 x 4 2, 4 x 3 x 2.5 3, 3 x 2 x 2 4, small	Enlarged prostate—contracture of vesical neck	Trabeculation	Ureter transplanted—3 sacs resected—punch operation. (Prostatectomy two years previously)

Judd, E.

*All Males

In the 13 cases with multiple sacs, of which one or more were large, one of these was always considerably larger than the others associated with it and in 9 of the 13 a definite condition of obstruction, other than the diverticulum, was recognized. The bladder was trabeculated and hypertrophied in all.

A review of the case reports, in which are given histologic studies of the diverticulum, shows that a classification into congenital and acquired types on the basis of Englische's differentiation cannot be made. The wall of every pouch studied contained smooth muscle fibers usually arranged in bundles intermingled with connective tissue. Fatty degeneration, elastic fiber substitution and leucocytic infiltration are prominent. The muscle is sometimes described as existing in layers cut transversely and longitudinally. A mucous membrane is commonly present, which is often partially absent and either transitional or flat. The thickness of the wall varies from 0.5 to 5 mm., and a frequent observation is the variation in thickness of the wall of an individual diverticulum, an apparently thick walled sac having areas of transparent thinness.

Conditions of obstruction. In table 5 are enumerated the findings with respect to obstruction to urination, of which prostatic hyperplasia (56 cases), contracture of vesical neck (11 cases), urethral stricture (11 cases), and vesical calculus (14 cases—4 associated with hyperplasia) are the most frequent. Of the 190 cases reviewed the reports of many are so incomplete as to justify doubt of the absence of urinary obstruction. Nevertheless in over 50 per cent of the cases reported in the literature no evident condition of obstruction other than the diverticulum is recognized.

Sixteen cases had led catheter lives from three weeks to fifteen years, the average duration being over four years. Among these cases there are 6 in which no obstruction is mentioned and only 4 associated with prostatic hyperplasia, whereas 5 of the 11 cases of contracture of the neck have led catheter lives.

The amount of residual urine is given in 50 cases. Hagner reports a complete retention of 4320 cc. in a man of seventy-four with an enlarged prostate. There were 10 cases with residual

urine of over 1 liter; three of these had enlarged prostates and two contractures of the vesical neck. Thirty cases had less than 500 cc. residual urine. The frequency with which residual urine persisted following excision of the diverticulum is noteworthy. This in a number of cases was relieved after a secondary operation upon the vesical neck (table 6).

TABLE 5
Conditions of obstruction to urination

CONDITION	CASES
Obstruction wanting.....	93
Prostatic hyperplasia.....	56
Prostate "enlarged".....	38
Prostate "small".....	12
Prostate "fibrous".....	4
Prostate "large".....	2
Contracture of vesical neck (median bar).....	11
Urethral stricture.....	11
Stricture of meatus.....	1
False passage in posterior urethra.....	1
Congenital posterior urethral valve.....	1
Caruncle at meatus.....	1
Vesical calculus (4 with enlarged prostates).....	14
Tabes.....	1
Calculus in diverticulum.....	5
Tumor in diverticulum.....	6

ANALYSIS OF TWENTY-ONE PERSONAL CASES

Within four years the writer has seen 21 cases of vesical diverticulum which is evidence that the condition is not as rare as generally believed. The youngest is thirty-seven, the oldest seventy-seven, the average age fifty-six. There are two women. A study of these cases would tend to disqualify diverticulum as a distinct clinical entity. Three of the cases noted suprapubic masses which would disappear upon voiding and a few noted at times almost an immediate refilling of the bladder after voiding. But otherwise the onset, course and termination duplicate in general the clinical picture of any severe prostatism. That infection rarely instituted symptoms is shown in table 7. Cloudy

TABLE 6

Poor results that have followed removal of diverticulum with no treatment of condition of obstruction

AUTHOR	AGE	CONDITION OF OBSTRUCTION	RESIDUAL	TREATMENT	RESIDUAL AFTER TREATMENT	SECONDARY TREATMENT	REMARKS
	<i>years</i>		<i>cc.</i>		<i>cc.</i>		
Englisch	60	None	200	Catheter life			
Wulff	34	None	1000	Excision			
Young, H. H.	66	Prostate	400	Division of septum			
Young, H. H.	30	Contracture of vesical neck	330	Excision		Bottini	No residual
Berry	21	None	510	Excision, perineal drainage			
Joly	51	None	390	Excision		Young's Punch	90 cc. residual
Joly	53	Stricture	360	Eversion			Suprapubic fistula after three months
Lerche	38	Contracture of vesical neck	200	Excision		Young's Punch	No residual
Beer	35	None	600	Transperitoneal excision			
Barney	56	Small prostate	1500	Excision of diverticulum	1200		Still uses catheter
Lower	49	None	300	(1) Cystotomy			Examination after two years shows reformation of diverticulum
			Retention	(2) Partially resected			Improved
Lewis and Moore	39	Contracture of vesical neck	840	Excision		Put on posterior urethral dilatations	Improved
Schussler	23	Contracture of vesical neck (diagnosed three months after excision)	1000	Excision		Litholapaxy — urethral dilatations	Improved
Schussler	43	None	?	Excision			Retention—still uses catheter 3 times daily

TABLE 7

Personal cases grouped with respect to type of prostatism and to show the relation of initial symptom to onset of pyuria

CASE NUM- BER	AGE	INITIAL SYMPTOM	TIME OF ONSET OF	
			Initial symptom	Pyuria

Contracture of vesical neck, 13 cases

	years		years	years
1	57	Frequency and difficulty.....	20	20
2	67	Hesitancy and difficulty, pain in bladder region.....	27	5
3	56	Difficulty.....	20 to 30	4
4	55	Complete retention following straddle injury.....	10	10
5	37	Difficulty.....	5 to 10	5
6	54	Pyuria.....	5	5
7	46	Urgency and nycturia.....	25 to 30	None
8	51	Frequency and difficulty, pain in left lumbar region.....	15	None
9	67	Frequency and difficulty.....	10	2
10	75	Frequency.....	since youth	5 to 6 wks.
11	74	Acute retention.....	1	None
12	50	Pain in right side on bladder distention.	17	None
13	45	Diminution in urinary force.....	1	None

Prostatic hyperplasia, small fibrous type, 4 cases

14	70	Difficulty and frequency.....	About 10	10
15	71	Acute retention as result of urethral stricture.....	20	1 to 2
16	55	Frequency and burning.....	8	Few
17	62	Difficulty and frequency.....	2 to 3	None

Prostatic hyperplasia, glandular type, 2 cases

18	68	Frequency and difficulty.....	5	1 to 2
19	69	Painful and frequent urination.....	17	12 to 15

In women, 2 cases.

20	40	Frequency, pain, burning.....	20 to 30	20 to 30
21	56	Frequency, pain, burning.....	15 to 20	15 to 20

urine was first noted on an average of six years and was absent altogether in 5 cases, whereas, the average duration of symptoms since onset is sixteen years. Undoubtedly symptoms of obstruction were aggravated in many cases by the diverticulum but it seems doubtful that the long periods of difficult urination were the result of the diverticulum from the beginning.

An unusual finding is the frequency of contracture of the vesical neck, 13 cases. No doubt all of these cases would be regarded by most urologists as congenital types. Operations to relieve the obstruction due to contracture were required in 8 of these cases. In the earlier and some of the later cases the significance of contracture was not realized and Punch operations, after the method of Young, were performed weeks or months after the radical resection of the sac in order either to secure suprapubic closure or to relieve persistent and often considerable residual urine. In two cases secondary Punch operations were necessary. The attendant success in the 8 cases proves the effectiveness of the contractures.

Hyperplasia of the prostate complicated the condition 6 times but it was of the glandular type in only two and in neither of much size. In 4 cases there were small fibrous or collar hypertrophies, in three of which multiple prostatic stones were present.

Seventeen cases have come to operation (radical extraperitoneal resection in each) and 22 diverticula have been removed. In these cases in which the number and position were determined by direct examination in confirmation of cystoscopic and x-ray studies, a single large diverticulum was present in 11 cases; two in 4 cases, and 3 and 4 each, in 1 case. In figure 1 is graphically shown the relative position of the orifice of the 22 pouches. In not one instance was the region of one or the other ureteral meatus uninvolved. Trabeculation of the bladder was a prominent finding. The relation of dilated ureters and of deep cellulæ is striking, table 8, some of these cellulæ were really small diverticula. Only those are noted which at operation admitted the tip of the gloved finger for about 2 cm. In 9 of the 11 cases of single sacculation a deep cellule was located near the opposite ureter, and in the base in 3 of the 5 instances of multiple diverticula.

Careful histologic study fails absolutely to differentiate the 22 specimens into two groups (table 9). The walls of all show marked variation in thickness. When held up to the light after fixation, thin, almost transparent areas are seen in each one. Smooth muscle bundles intermingled with connective tissue

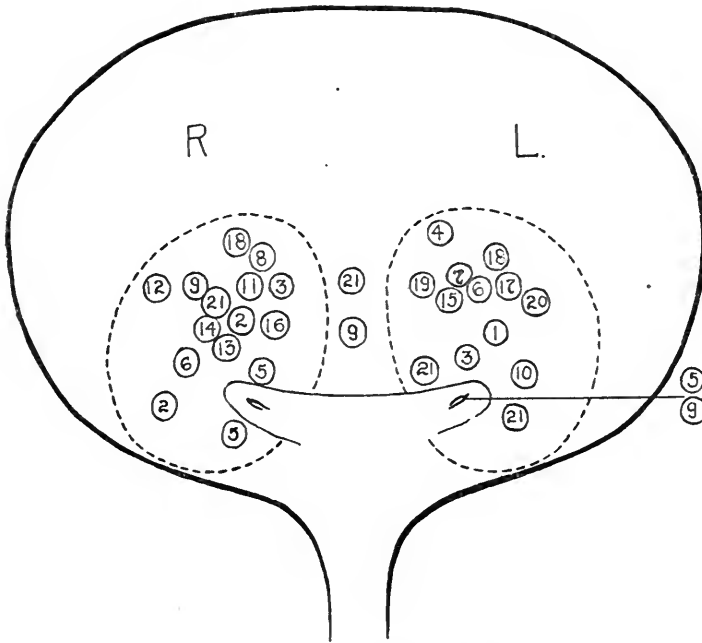


FIG. 1. GRAPHIC REPRESENTATION OF THE RELATIVE POSITION OF DIVERTICULAR ORIFICES IN TWENTY-ONE PERSONAL CASES

Cases nos. 2, 3, 5, 6, 9, 18 and 21 have multiple diverticula. The only instances in which the base was involved are in two of these (9 and 21). A ureter opened into a diverticulum in only two instances and again both were cases (5 and 9) with multiple sacs.

bands are present in the walls of each sac and in many even of the largest the connective tissue out-proportions the muscle. The muscle fibers are cut sometimes transversely, sometimes longitudinally, and often obliquely, but no arrangement into three definite layers as found in the bladder can be found. There is a remarkable absence of epithelial lining in all of the sacs which

TABLE 8

Location of diverticula and relation to large cellules and dilated ureters

CASE NUMBER	RIGHT URETERAL AREA			BASE OF BLADDER ABOVE LIGAMENTUM INTERURETERICUM		LEFT URETERAL AREA		
1		C	U			D		
2	DD						C	
3	D				C	D		
4		CC				D		
5	DDD		U			Du		U
6	D		U		C	D		
7						D		
8	D						C	
9	D			D	C	Du		U
10		C				D		U
11	D				C		C	
14	D							
15		C				D		
16	D							
17		C				D		
18	D	C				D		U
19		C			C	D		

TABLE 9

Size of diverticulum and thickness of wall

SIZE OF DIVERTICULUM		THICKNESS
	<i>cm.</i>	<i>mm.</i>
1	11.0 x 10.0 x 10.0	5.0
2	10.0 x 8.2 x 10.0	2.0
3	5.0 x 4.8 x 4.0	1.0
4	8.5 x 7.0 x 6.0	2.8
5	4.2 x 3 x 3	1.0
6	5 x 4 x 4	3.0
7 }	10 x 7 x 9	1.2
8 }		
9 }		
10	11.0 x 10.0 x 14.0	2.5
11	12.0 x 11.0 x 10.0	3.0
12	7.0 x 7.0 x 6.0	2.0
13	6.0 x 6.0 x 4.0	1.5
14	8.0 x 7.5 x 7.0	2.5
15	5.0 x 5.0 x 4.0	6.0
16	4.0 x 3.0 x 2.5	1.5
17	3.0 x 2.0 x 2.0	0.25
18	3.0 x 2.0 x 2.0	1.0
19	4.0 x 3.7 x 3.0	1.0
20	5.0 x 6.0 x 4.0	2.0
21	4.0 x 3.5 x 3.0	2.0
22	3.0 x 3.0 x 2.0	1.0

may be the result of surgical trauma, as they were all packed with gauze to facilitate removal. In the one case with a mucosa a thin pavement epithelium unlike bladder mucosa was present.

THE PATHOGENESIS OF AN ACQUIRED DIVERTICULUM

At least three definite factors in the production of an acquired diverticulum can be inferred from the evidence as presented. These may be described as anatomic, pathologic and mechanic.

a. Anatomic. The structure of the bladder is such as to predispose its wall to localized herniation. The inner and outer longitudinal layers are imperfect coats, being made up of interlacing bundles of smooth muscle. With hypertrophy of the bladder this reticular formation, particularly of the inner coat, is increased so that certain small portions of the wall possess only the middle transverse layer with loose imperfect bundles from one or the other longitudinal coat. The areas of ureteral perforation of the bladder are more or less fixed parts so that the walls of the bladder in the immediate neighborhood are subjected to more than usual tension, and are bent and pulled back and forth with vesical distention and evacuation, thus tending to aggravate the reticulation. Trabeculation in any bladder is always most pronounced and often confined to the region above the ureteral orifices and the ligamentum interuretericum (fig. 2). This is certainly not the result of local weakness as shown by the histologic studies of Sugimura and others who have demonstrated that in infants the transverse layer of muscle is even strongest at and above the points of union with the trigone. The anatomic arrangement of the inner longitudinal muscle layer in its relation to the fixed area of the trigone renders this portion of the bladder functionally predisposed to herniation. As is well known, anteriorly and laterally the bladder walls have a greater and more uniform freedom of movement.

b. Pathologic. Changes in the bladder wall leading to muscular insufficiency at points of anatomic weakness and urinary back pressure which will aggravate it, constitute the pathologic

factors in the production of diverticulation. The bladder walls may be altered by processes of compensation, sclerosis and inflammation. In the normal bladder elastic fibers are relatively few in number but with the changes incident to compensatory hypertrophy they correspondingly increase. At about the age of fifty certain atrophic changes, irrespective of hypertrophy, occur in the bladder muscles and hand in hand an increase in the interstitial connective tissue and the elastic fibers will be

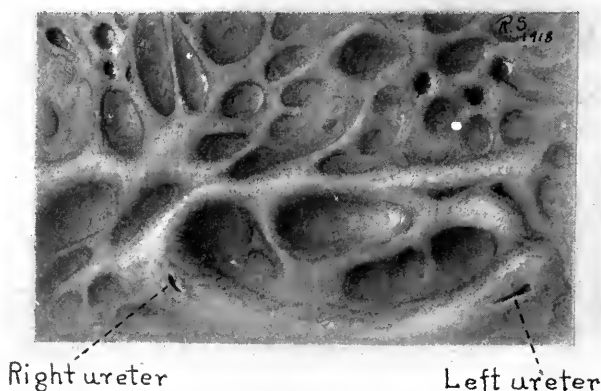


FIG. 2. DRAWING OF THE CYSTOSCOPIC APPEARANCE OF THE BLADDER OF A YOUNG MAN OF TWENTY-EIGHT WHO HAD NEVER HAD URINARY SYMPTOMS

Urologic study was made to determine the cause of renal colic and an ureteral stone was found. There was a slight median bar but no residual urine. Several deep sphincter-like orifices are seen above each ureter. Above the ligamentum interuretericum are broad diffuse cups. The former are more probably precursors of diverticula than the latter.

noted. The elastic tissue growth compensates the muscle atrophy. Arteriosclerotic changes in the larger blood vessels no doubt often exist. Either may occur only locally. Finally, inflammatory processes frequently institute or aggravate such local connective tissue substitution.

c. Mechanical. Any condition of obstruction demanding an increased effort on the part of the bladder will materially exert a mechanical effect on the above stated changes in its wall. Long continued compensation from mild obstruction is more apt to

produce greater localized changes than relatively quick and severe obstruction which rapidly leads to a general vesical dilatation before any considerable compensatory changes have occurred. Once a local point of weakness in the transverse muscle layer in the gap of trabeculation of hypertrophied longitudinal fibers has begun to bag from the increased and repeated intra-



FIG. 3. CYSTOSCOPIC APPEARANCE OF THE BLADDER OF CASE 11, AGE SEVENTY-FOUR, WHO HAD NO URINARY COMPLAINT UNTIL THIRTEEN MONTHS AGO WHEN SUDDEN RETENTION OCCURRED

He has led a catheter life since. The bladder wall, laterally and posteriorly, shows trabeculation and cellule formation. A definite fibrous bar is seen traversing the bladder above and parallel to the interureteral ridge and above this is a broad deep pouch. Both ureters are seen and above each and externally are numerous well marked orifices. At operation only two of these admitted the tip of the gloved finger. Each lay about 3 cm. above the respective ureter. Their necks were dilatable but thick and their walls very elastic and distensible. The larger (right) was removed by the inversion method of Young. The others seemed too insignificant to demand treatment. At the vesical neck was a pronounced fibrous median bar, so tight as to prevent insertion of the finger into the posterior urethra. There was no prostatic enlargement. Median bar destroyed by cauterization—cure.

vesical pressure two additional mechanical factors may be conducive to its growth. The hypertrophied longitudinal bands between which herniation occurs form a sphincter-like orifice which contracts but never completely closes on evacuation of the bladder. This constriction nullifies the effort of the local transverse muscle layer just inside its orifice. The local and incomplete constriction prevents efficient action of the transverse fibers beneath and allows the full intravesical pressure to press against them at the very time of their weakened action. Buerger and Kelly have both emphasized the sphincter action of diverticular orifices. Another mechanical effect has to be thought of, namely, the narrowed orifice at the time of micturition will render greater the intradiverticular pressure; the mechanism being the same as is known to be active in obstructions of the vesical neck. Diverticulum formation rarely if ever occurs immediately above the ligamentum interuretericum and yet autopsy specimens of long continued back-pressure often show marked thinness and local distention in this area (see fig. 3). The very fact of its broad diffuse nature probably protects it from greater herniation.

DISCUSSION

In my experience the clinical facts strongly support the above explanation. The exceptional occurrence of the condition in youth and in women is striking. Reference to the tables in which these few cases are analyzed shows that the majority had recognizable conditions of urinary obstruction and that the diverticula present differed in no way in structure or position from those found in old men.

The preponderance of the localization of the orifice in the neighborhood of ureteral meati is equally striking. In this area trabeculation and cellule formation is always most marked. The relative frequency of large cellules near the opposite ureter in instances of a single diverticulum, or, in the base of double diverticula, stands as proof of a progressive change from back-pressure. This conclusion is in part supported by the finding of hydroureters. Even stronger evidence is presented in the

observation illustrated by the accompanying cystograms (figs. 4, 5, and 6), namely, the hydroureter together with a large cellule occurred near the opposite ureter. A recent autopsy specimen illustrates the same point, a dilated ureter on the side opposite to the diverticulum, and a normal undilated ureter on the same side. A single dilated ureter on the same side as the diverticulum is more often the result of local ureteral obstruction from the distended diverticulum than from the general vesical obstruction.



FIG. 4. PLAIN CYSTOGRAM OF LARGE SINGLE DIVERTICULUM OF CASE I

Showing a large diverticulum on the left and a hydroureter and small cellule on the right.

The structure of the walls of diverticula are exactly what one would expect in a local herniation which has taken years to develop. The interlacing of muscle bundles with connective tissue which often predominates, the marked variation in thickness in the wall at different places, and the often considerable granulation, all readily conform to my conception.

The relation of diverticulum formation to prostatism is suggestive and emphasizes one factor heretofore not sufficiently recognized, namely, that a mild long continued obstruction is

more potent in its production than a more rapid and complete obstruction. If this be true, diverticulation should complicate contracture of the vesical neck more often than prostatic hyperplasia. Our personal experience offers information concerning this point. Of 21 cases, 13 had median bars and 4 others had small fibrous or collar hypertrophies. Only 2 had large glandular hyperplasia. Of the cases reported in the literature in association with enlarged prostates, the majority also had small or fibrous prostates. The relatively few cases of median bar that



FIG. 5. CONTRAST CYSTOGRAM OF CASE I

The bladder has been filled with air after catheter drainage. The diverticulum, cellule and hydroureter have remained full of thorium solution.

have been reported implies failure to recognize the condition. Such a view is supported by the numerous cases in which poor results following excision of the sac were remedied by subsequent treatment of the contracture, (Young, Chute, Bransford-Lewis, 4 cases of the author) and by the statistics of Randall, Young and others. Randall, in 300 autopsies taken at random with ages varying from 18 to 83, found 54 median bars, or almost one-fifth of the number, not all of which, however, showed marked evidence of obstruction, but in 6 per cent evidence of urinary

obstruction, such as trabeculation or true diverticula, was found. Young's study of 156 cases of median bar reveals 23 cases with diverticulum, or 15 per cent, and marked trabeculation in 43. In a personal experience with 132 prostates, diverticulum occurred in only 6 or 4 per cent, and 4 of these were of the small fibrous type, more comparable to median bar than hyperplasia.

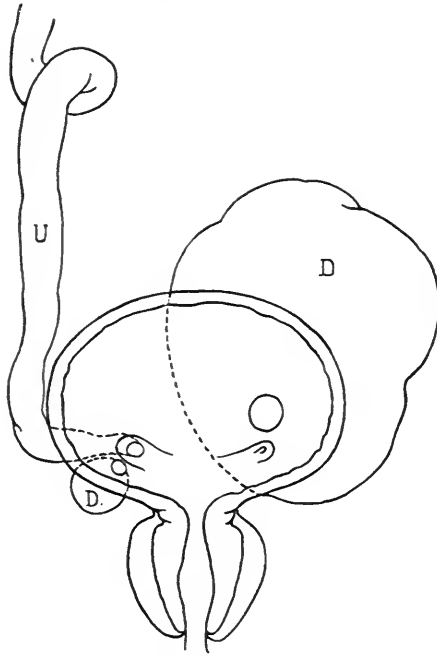


FIG. 6. DIAGRAM OF CONDITIONS IN CASE I

It is reasonable to infer that the diverticulum, cellule and dilated ureter are all three the result of the median bar at the vesical neck. There was no prostatic hyperplasia.

The duration of symptoms in median bar cases is also suggestive in this connection because it complies with the chronic mild type of obstruction necessary for diverticulum formation.

In Young's 156 cases³ the duration of symptoms averages over twelve years.

³ Ten of these cases are not median bars. Three had carcinoma of the prostate and 6 vesical polyps, and 1 a cyst of the vesical orifice.

	Cases
Under 1 year.....	11
1 to 5 years.....	50
6 to 10 years.....	32
11 to 20 years.....	28
21 to 30 years.....	4
31 to 45 years.....	2
Since childhood.....	13
Not stated.....	17

More than half of the cases had had symptoms for more than five years, a period similar to that of the cases of diverticulum analyzed by the author (see above page 214). That urinary

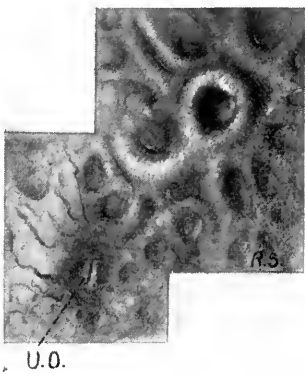


FIG. 7. SMALL SPHINCTER-LIKE ORIFICE OF A SHALLOW CELLULE IN A CASE, AGE FORTY-TWO, OF VESICAL POLYPI WHO HAD SUFFERED WITH PAINFUL AND FREQUENT URINATION FOR ABOUT FOUR YEARS

This might well be the precursor of a diverticulum.

obstruction of considerable degree may be present for years without symptoms is well known. No doubt trabeculated and thickened bladders can be encountered in individuals who have never had an urinary complaint. The bladder has fully compensated for the obstruction but as time goes on and pathologic changes supervene, evidences of bladder insufficiency begin and the bladder dilates generally (fig. 9) or locally (fig. 5).

The incidence of diverticulum, median bar and prostatic enlargement by decades is most interesting and is therefore shown graphically in the accompanying chart (fig. 8). As will

be noted the curves for median bar and diverticulum almost parallel each other, while prostatic enlargement occurs at a definitely later period.

It would seem then that the slow, prolonged, rather mild type of obstruction produced by median bar is particularly effective in the production of a diverticulum. An anatomic or pathologic weakness in the bladder wall is required for this effect to occur.

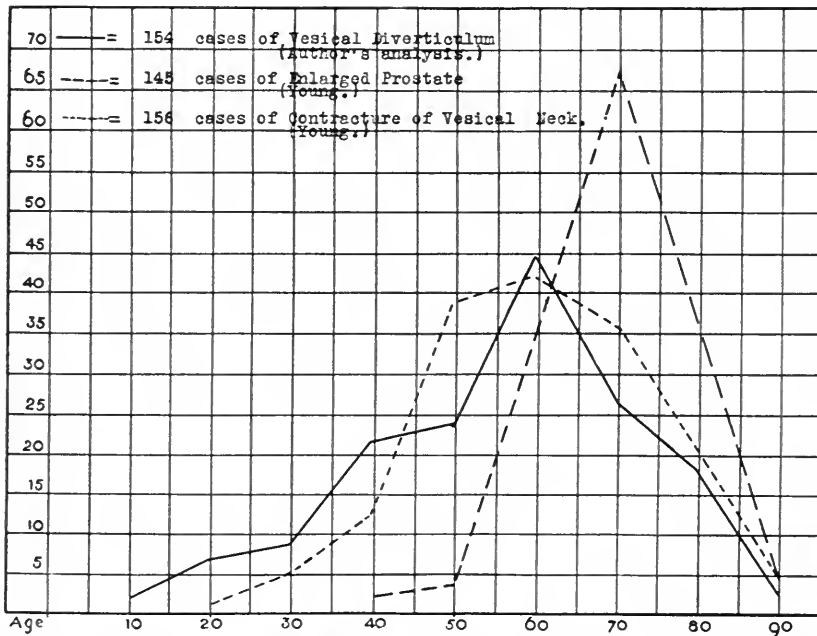


FIG. 8. CHART SHOWING INCIDENCE BY DECADES OF VESICAL DIVERTICULUM, PROSTATIC HYPERPLASIA, AND CONTRACTURE OF THE VESICAL NECK

When not present vesical dilatation and bilateral hydroureters and hydronephroses may develop.

Undoubtedly a diverticulum itself may obstruct the vesical outlet. The sacs are almost all posterior and when they reach a certain size are forced by intra-abdominal pressure to dissect their way downward between the rectum and prostate, so that upon distention they would obstruct the vesical neck in much the same way as an intravesical prostatic lobe. This probably

accounts for the large residual urine, frequent retention and the rather high percentage of cases leading catheter lives.

What evidence is there for a belief in the congenital origin of a vesical diverticulum? The writer finds none, clinically or anatomically. The fact that women rarely have the condition does not disprove its acquired nature and of this I am more convinced after having cystoscoped a number of female bladders

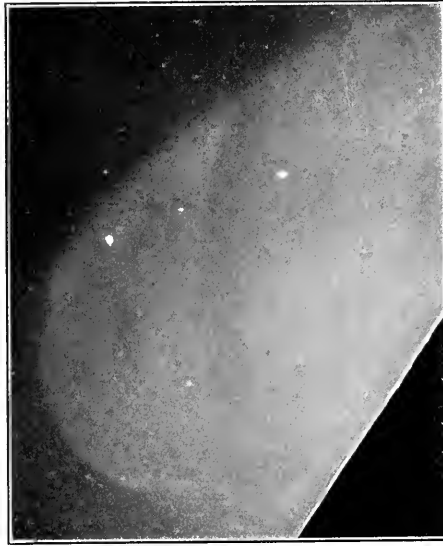


FIG. 9. CYSTOGRAM OF CASE WITH RETENTION OF 1200 CC.

Catheter life for four months. Pronounced median bar but no prostatic enlargement. Bladder trabeculated and sacculated, but no true diverticula. Irregular outline of bladder shown in cystogram. Thoroughly explored at time of cystotomy. Median bar resected. Cure.

with trabeculation and cellule formation comparable to that of a prostatic. A recent case in a woman of fifty-six gave an interesting history of difficulty since childhood and the cystoscope revealed a markedly trabeculated bladder with many deep cellules located above the ureters and in the base in every way analogous to that found in the male. There were a few small edematous polyps in the urethra and a reddened painful caruncle at the meatus, with absence of urinary infection.

The idea of accessory ureteral buds or vestigial Wolffian ducts as cause for diverticula gains no support by this analysis. As is known their location is always in the line of the ureteral ridge. On the other hand blind ureteral sacs have been reported (Joly, Thomas). The accompanying illustrations will demonstrate a

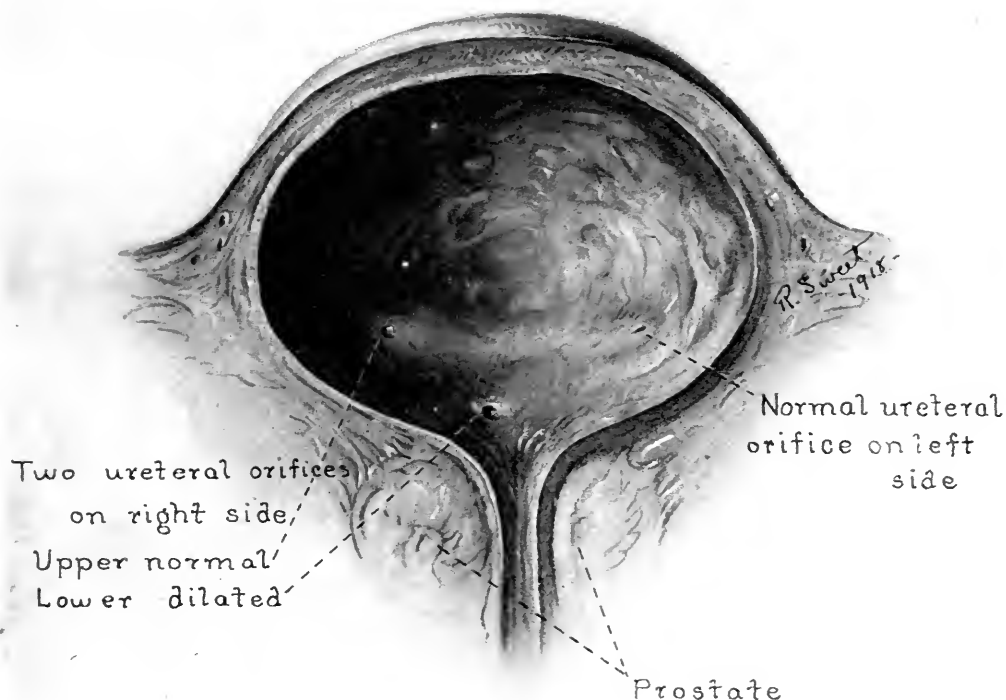


FIG. 10. DIAGRAMMATIC DRAWING OF CASE WITH BLIND URETER IN MAN OF TWENTY-NINE

No urinary history, but marked pyuria.

similar case in a young man of twenty-nine seen by the author. The bladder in this case was not trabeculated. There was no cellule formation and the only noteworthy thing cystoscopically was a third ureteral orifice which, as shown by x-ray, led to a blind ureter (figs. 10 and 11).

The inclusion of an ureteral orifice in the wall of a diverticulum can readily occur as a mechanical result of back-pressure, the ureter being drawn in with enlargement of the sac. Thus far only 12 cases have been reported (see table 4). It is evident from the table that the majority has been associated with multiple sacculation and conditions or evidence of obstruction were present in all. They cannot form a recognized argument



FIG. 11. CYSTOGRAM OF BLIND URETER CASE

Long sausage-like sac curves parallel to the ureter to end blindly at the edge of sacrum.

for congenital formation. Knauf's case in which each ureter opened into separate large diverticula is remarkable. Each had thin walls and this fact and their peculiar relation to the ureters has led Knauf to advance the idea of their ureteral, rather than vesical origin. Case V with 4 large diverticula, into one of which an ureter opened, is even more remarkable (figs. 12, 13 and 14). But even these four unusual sacculations appear to have been acquired.

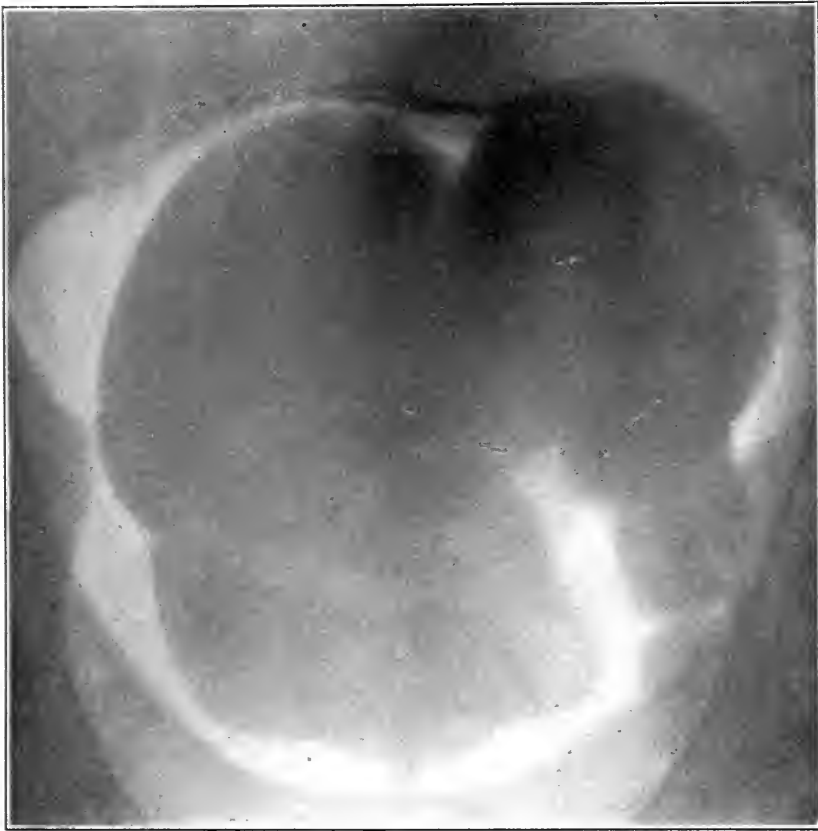


FIG. 12. CYSTOGRAM OF CASE V (SEE TABLE 8)

Age thirty-seven. Frequency and difficulty for many years. Pyuria five years; catheter life for three years. Three multilocular diverticula on the right with two openings into the bladder as shown in figure 13. Large single diverticulum on the left side with left ureter opening into it. Marked median bar. Bilateral hydroureters and pyonephrosis. Total phenolsulphonphthalein 12 per cent in two hours. Extraperitoneal excision of all, the specimens being shown in figure 14. Young's flap operation on left ureter, transplantation of right. Division of median bar. Failure of suprapubic fistula to close permanently in six months. Second urethral punch operation—fistula closed very soon. Urination normal; up two to four times at night; no dribbling or pain. Control perfect. Urine still purulent. Returned to heavy work in warehouse.

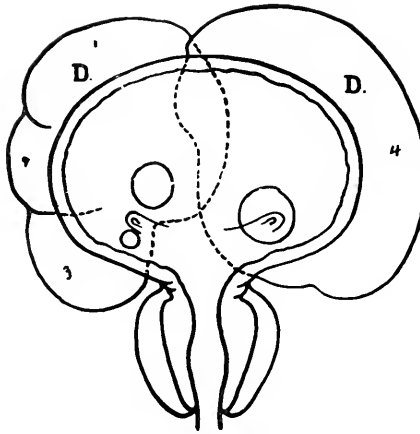


FIG. 13. DRAWING OF CONDITIONS IN CASE V

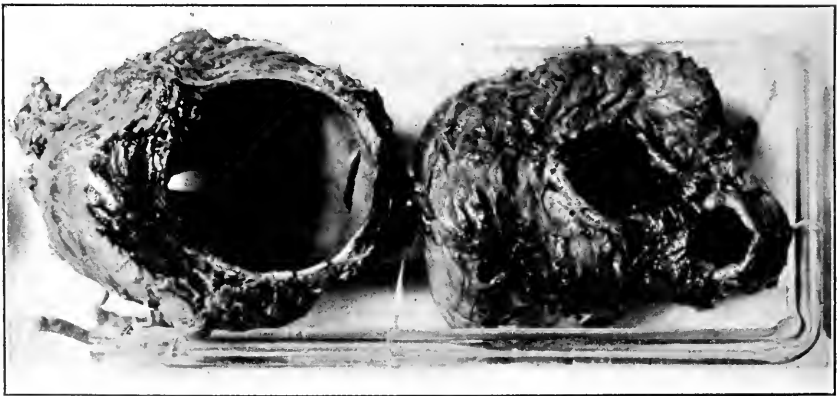


FIG. 14. PHOTOGRAPH OF SPECIMENS REMOVED IN CASE V

The experimental failure to produce a vesical diverticulum is of little value in this discussion. In the light of our explanation the proper experiment has not yet been performed.



FIG. 15. CYSTOGRAM OF CASE WITH SINGLE DIVERTICULUM

The sharp, even outline of the sacculation contrasts markedly with the rough irregular vesical shadow: Male, with median bar.

CONCLUSIONS

Vesical diverticulum is the result of anatomic, pathologic and mechanical factors in the vast majority, if not all instances, and in this sense is always an acquired condition.

A mild and chronic urinary obstruction in association with the necessary anatomic or pathologic predisposing conditions of the bladder wall is particularly conducive for the development of diverticula. Median bar formation is one of the most frequent types of obstruction.

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JARECKI	ZACHRISEN

HISTOLOGIC STUDY OF THE URETER

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Before describing a study of the physiology of the ureter, which will be published in the American Journal of Physiology, it seemed desirable to make as complete an investigation as possible of the structure of this organ, since the exact physiologic action cannot be explained unless the anatomic structure is understood. In regard to the movement of the ureter, for instance, some authors have considered that the muscle tissue itself has the power to initiate contractions at certain points and transmit them in the form of a peristalsis or anti-peristalsis. They inclined to this view because they were unable to demonstrate a nervous supply in all parts of the ureter. On the other hand, other writers state that there are nerve plexuses and ganglion cells in every part of this organ, and that its movements depend entirely upon this nerve supply.

In this paper will be described especially the structure of the muscle layers, the nerves and epithelial glands—the first two because they have to do with contractions of the organ, and the last because it may have an influence upon the composition of the urine.

In carrying out this work normal ureters of the cat, dog, pig and human being were employed. The human ureters were obtained from the Department of Pathology and were secured at autopsies from a baby, a youth and a middle aged man. All materials were fixed in 10 per cent formalin or alcohol and imbedded in paraffin for serial sectioning. Each series of sections represented an entire organ. Some of the sections were stained with hematoxylin and eosin, others by Van Gieson's method, others with fuchsin for elastic fibers and finally some with toluidin blue for nerve elements. Other methods of fixing and staining were used to study the nervous supply especially as will be described later.

DESCRIPTION OF THE LAYERS

1. The outer fibrous coat

This coat is of a very variable thickness and is composed of areolar connective tissue and a few elastic fibers which follow no definite arrangement. At its lower end is found a group of longitudinal muscle fibers located on one side which is known as Waldeyer's ureter sheath, as he was the first to describe it (plate 1, figs. 4 and 5, *w*). It can be seen especially well developed in the ureter of the middle aged man. The muscle bundles increase gradually in number and size, from above downward some of them changing their course and becoming transverse. At the intraparietal portion of the ureter these fibers join the muscles of the bladder. In other words, a number of the muscle fibers of the bladder wall ascend along one side of the tube as a process. Between this muscle group and those of the proper muscle layer of the ureter, there is interposed a large amount of connective tissue together with large nerve trunks and blood vessels, which are not found within the proper muscle coat (plate 1, figs. 4 and 5, *bv*). Moreover the outer fibrous coat is the seat of large blood vessels and nerve trunks, which give off many branches that form a network of large, rhomboid meshes.

The ureter is situated retroperitoneally and is in contact with the peritoneum along its whole course. Where the peritoneum touches the ureter the connective fibers become thicker in the form of bands, constituting apparently special connections between the ureter and peritoneum. These structures are developed more distinctly in the lower half of the ureter, so that the course of the lower part can be found with less difficulty in the abdominal cavity even in the presence of a large quantity of the periureteral fat. These band-shaped connective fibers seem to function as attachments of the peritoneum to the ureter, because the ureter in its lower part has a close relationship with the peritoneum in its blood supply from the spermatic arteries.

2. *The muscle coat*

Muscle fibers occur in bundles of different size interspersed with varying amounts of connective tissue. This coat makes up one-half or more of the whole thickness of the wall and is variable in thickness at different levels, being thicker in the middle portion and decreasing gradually toward each end. This gradual diminution in thickness is more pronounced in the upper than in the lower third, so that the ureter has the thinnest muscle coat at the upper end where it continues into the renal pelvis. In the renal pelvis the muscle coat becomes a little thicker again.

Concerning the course of the muscle fibers, Sappey asserts that the muscle fibers are not arranged in strictly circular and longitudinal courses, but the bundles of fibers run in different directions making only one layer, which has a braided structure. Diesselhorst finds the same structure of the muscle in the human ureter. Rud. Maier, Krause, Obersteiner, Frey, Mayer and others distinguish three layers: two thin longitudinal and a middle circular. But according to Krause the outer longitudinal layer disappears in the upper quarter of the ureter. On the other hand, Luscka, Henle, Kutschitzki, Hesshing, Radash and others describe only two layers: an inner well developed longitudinal and an outer weak circular coat. Peremaschka and Stoehr in addition noted an interrupted layer of outer longitudinal fibers in the lower half of the organ. According to Koelliker, the muscle coat consists of outer longitudinal and inner circular fibers and at the bladder end still other inner longitudinal fibers. Engelmann, investigating the ureters of the rabbit chiefly, distinguishes two layers but the arrangement of the muscle fibers in the layers becomes irregular at each end, especially at the bladder end.

According to Protopopow's description of the structure of the ureter there are three definite muscle layers: two longitudinal and one middle circular. The outer longitudinal coat is very weak, the inner longitudinal one is stronger, while the middle circular coat is the best developed. The circular coat forms an unbroken tube varying in thickness at different levels of the organ, the thickest portion being at the lower end; the diameter

decreasing gradually toward the kidney. In addition to the muscle layers described Protopopow observed oblique fibers, especially in the upper part.

Microscopic examination of the ureter has shown that the course of the muscle fibers is quite different at the several levels, so that in some sections the muscle layers are very distinct, while in sections from other parts there are no definite layers. This fact seems to account for the divergence of the findings of many investigators as described above, since apparently a thorough examination of the entire ureter has not been made. In this work, therefore, serial sections were examined successively throughout the whole length of the ureter.

The lower part of the renal pelvis has a somewhat thicker muscle wall than the upper end of the ureter. Here the muscle fibers are chiefly circular. The inner longitudinal muscles are poorly developed, so that there can be seen only a few cross-sections of muscle bundles scattered in the submucosa. The muscle fibers of the outer longitudinal coat are bound together into a few quite large bundles, situated always on one side of the wall. These two longitudinal layers are relatively well developed in the human ureter and less well developed in the ureter of pig, dog and cat. On the other hand neither outer nor inner layers of longitudinal fibers are observed in the human baby.

The upper end of the ureter has an extremely thin muscle wall made up of fibers running in irregular oblique directions, so that layer formation is not distinct. The muscle fibers also are bound into relatively small bundles, which are separated by relatively large amounts of connective tissue. In the cross-section, therefore, this portion is quite different from others. The muscle bundles being cut obliquely in short stretches are placed parallel to each other in the connective tissue with relatively wide spaces between (plate 1, fig. 1).

The isthmus of the ureter in its upper half has almost the same structure as that of the upper end, but all of the fibers take a more circular course downward, so that they form a well developed circular coat at the lower end of the upper third. At the same time there appear some longitudinal fibers inside the oblique

muscle fibers. Thus in the lower half of the isthmus two layers may be distinguished with less difficulty—the inner longitudinal and the outer circular (plate 1, figs. 2, *il*, *c*). Besides these two layers a few cross-sections of muscle fibers bound into small bundles appear outside or sometimes in between the bundles of the circular layer. These fibers indicate the beginning of the outer longitudinal coat as an additional layer. They also begin at different levels of the tube in different animals. In the dog this outer longitudinal coat begins to appear at the isthmus and is markedly developed even at the lower end of the upper third, the tube being almost completely surrounded by this coat. On the contrary, in the pig the outer longitudinal layer first begins to appear at the middle part of the organ. In the human ureter the outer longitudinal layer is seen first at the upper end of the middle third, but I have seen no outer longitudinal fibers even at the beginning of the lower third in the human baby. The cat has almost the same arrangement of the muscle coat as the human being in this section.

At the lower end of the upper third the layer formation is quite different in animals and human beings. This difference is due to the beginning of the outer longitudinal layers as mentioned above and the proportions between the amounts of the muscle fibers of each layer. For instance, in the dog there is observed an outer longitudinal layer developed so distinctly even at the lower end of the upper third, that it has nearly a half or more of the thickness of the circular coat, and the inner longitudinal fibers bound into relatively small bundles can be seen, but do not yet form a definite layer, for they lie scattered in the loose connective tissue. In the human ureter (except the baby's) the outer longitudinal muscle fibers are developed less than in the dog, and muscle bundles, bound into relatively large masses cover only one side of the tube. The circular muscle fibers of the human ureter form a markedly thick layer with small clefts between them. The human ureter also possesses quite a large number of inner longitudinal muscles which form almost an unbroken layer even though each bundle is separated by connective tissue. In the pig's ureter the inner longitudinal coats

are very weak, so that there can be seen no layer formation. No outer longitudinal layer is observed in the pig's ureter in this section, as it begins first at the middle part of the tube.

The middle part of all ureters (except the baby's) has three distinct layers—a well developed circular layer and inner and outer less developed longitudinal layers (plate 1, fig. 3, *il*, *c*, *ol*).

In the middle part together with the lower third, however, both longitudinal coats show generally a gradual increase downward in the amount of muscle fibers as well as in the size of each bundle, while the circular layer becomes weaker toward the bladder.

The lower end of the ureter excluding the intraparietal part has thus a large number of longitudinal fibers united into almost one layer, which seems to occupy the whole extent of the muscle coat. And there can be found some very weak circular bundles in the middle layer of this coat (plate 1, fig. 4, *l*, *c*).

In the intraparietal part the structure of the muscle coat is very interesting and presents a marked difference from the ureters at higher levels. There are found no circular fibers and only a strong longitudinal layer remains (plate 1, fig. 5 *l*). The latter coat also shows a gradual decrease downward in the number of fibers and in the size of bundles. Especially on the medial side the muscle decreases so rapidly that it disappears soon after entering into the bladder wall. In the lower half of this portion, therefore, the muscle layer makes a half circle surrounding only the outer side of the tube (plate 1, fig. 6).

At the level at which the lumen of the ureter opens into the bladder, this longitudinal layer disappears almost entirely. There is no indication whatever of a sphincter at this point to shut off the ureter from the bladder cavity. But the muscle fibers of the bladder wall, which cover this part of the ureter, compress the ureteral lumen during the distension of the bladder. In addition the contraction of the longitudinal muscle fibers along the outer side serves to effect a decrease in the size of the orifice and thus aids in preventing a reflux of the bladder content.

3. *The mucous coat*

In this coat the submucosa contains a nerve plexus directly under the muscle layer together with blood and lymph vessels. Numerous processes of connective tissue are directed toward the muscle layer, and are interposed between the muscle bundles. The ureteral lumen is covered with a stratified transitional epithelium in four to six layers, which has almost the same structure throughout the ureter. The first layer of the epithelium is composed of large polygonal cells. In some preparations made of the human ureter there are two different elements within a cell body, one superficial showing a faint color and another deeper part having fine granulations. This difference however, has not been observed in the cell body of the baby's ureter, the cells have a fine granulated body giving a uniform tint with eosin. Less polynuclear cells are found in the ureteral epithelium than in the epithelium of the bladder, and the size of each cell seems smaller than that of the bladder.

It is very interesting to cite the description by Dogiel, in which he says that granulated clumps hang from the surface of these cells in the bladder. He thought that the substance produced from these clumps served to coat the surface of the bladder wall thus preventing any irritating effect from the urine. I do not find any similar structure, which might suggest such a protective function on the surface of the epithelium of the ureter. But there are quite a number of epithelial cells, in which the superficial part projects as a pendulous clump into the ureter lumen.

The second and third epithelial layers comprise two or three strata of cells, which vary in form and size. The deepest fourth layer consists of a row of columnar cells.

THE EPITHELIAL GLANDS

On the question of the existence of mucous glands in the urinary tract (excluding the urethra) there is a distinct divergence in the statements of many authors. Some have published definite descriptions of mucous glands in the ureter and bladder,

while others find no existence even of down-growths of the epithelial cells into the mucosa. The secretory units form two groups, one being unicellular, the other multicellular. Schiffer-decker and List respectively described goblet-cells in the bladder of several amphibia, many of which had secretory plugs at their mouths. Unruh described branched alveolar glands in the renal pelvis, which according to Hamburger and Egli also exist in the ureteral wall. The hollow of the gland is entirely filled with a number of large polygonal and granulated cells "so-called gland-cells" or they may exhibit a slit-like lumen. Further, Koelliker, Henle, Virchow, Krause and Gegenbauer noticed glands in the bladder especially at the base. Brunn described cell-nests of transitional epithelial cells in the renal pelvis which, however, do not appear to have a secretory function.

Some of these cell-nests have no lumen, but many of them show narrow slits, in which, however, there is found no secretion. On each side of these cell-nests connective tissue is found in varying amounts. In the upper third of the ureter he observed the same structure of cell-nests, which are larger than those in the renal pelvis and have more divisions. Lubarsh states in his paper on ureteritis cystica, that he found an unbroken series of transitions between cell-nests and well developed cysts. He concludes that the cysts develop from the cell-nests, and considers a preëxistence of cell-nests as a necessary condition for the formation of the cysts in the ureteral wall. On the other hand, Toldt and Sappey described no mucous glands in the urinary passage. Aschoff reports that he could find no glandular structures, but cell-nests as Brunn has done.

In my careful examination there were found small down-growths of epithelium for a slight depth into the mucosa. But they seemed to be too shallow to be regarded as Brunn's cell-nests. Sometimes an isolated group of epithelial cells was observed within the connective tissue of the mucosa, especially in the sections made parallel to the longitudinal axis of the ureter. By following the serial sections one by one such a cell group grows larger in size and exhibits a hollow in the center, which is finally connected with the ureteral lumen. I can not deny,

therefore, that there may be found isolated cell-nests or down-growths of epithelium in the mucosa in cross-sections of the ureter, but in my findings, these are not more than would suggest cross-sections of mucous folds.

As regards unicellular glands I could find no goblet-cells in the ureter. But in some sections there are noticed cells which had a large and definite area staining pale in eosin.

LYMPHOID SYSTEM

Some authors as Hamburger, Radash and others found diffuse lymphoid tissue and even solitary nodules. Chiari, however, considered these as pathological products and never observed such structures under normal conditions. I found diffuse lymphoid tissue as well as nodules in the pig, and occasionally in the human ureter. They are located mostly in the mucosa and cause the mucosa to be elevated into the ureter lumen in the shape of a papilla, when they grow to a large size. In the pig's ureter they are extended into the muscle layer even to the outer fibrous coat. The pig's ureter which contained these numerous lymphoid nodules gave no evidence of being pathological and they showed very marked contractions in Locke's solution at a temperature of 37°C. for three days after removal. The human ureters were taken from cadavers which exhibited no morbid change in the kidney or the ureter.

NERVOUS SUPPLY

From the physiological point of view the most interesting question in the histology of the ureter is the structure and distribution of the nervous elements in the ureter wall.

Remark first in 1840 stated that he found peripheral ganglion cells in several organs of the alimentary canal and the urinary tract. Manz also found ganglia in the bladder of the frog and in the ureter of the bird. Engelmann was the first author to make a detailed investigation of this point. According to this investigator a number of nerves enter the ureter at two points; above, at the hilus renalis are a few branches from the plexus

renalis; and below, at the bladder end, a few somewhat larger branches arise from the sympathetic plexus. These nerve trunks build a plexus with large and long meshes in the outer fibrous coat along the whole length of the ureter. He called it "grund plexus." Ganglion cells are absent from this plexus except at the lowermost 3 or 4 cm. At the hilus renalis and in the renal pelvis there are occasionally found a few small ganglia. The ganglia in the lower sympathetic plexus contain a large number of cells. The ground plexus in the adventitia gives off numerous small branches inward to the muscle coat, the ends of which penetrate the mucosa. Some of these branches go still deeper and seem to terminate in the epithelium. There is an absence of ganglia or any thing resembling them in the mucosa. Dieselhorst demonstrated almost the same finding as Engelmann, in that he did not find any ganglia in the ureteral wall, excluding the lower part.

On the other hand, Dogiel found ganglion cells in the outer fibrous coat of the ureter of the dog, mouse, pigeon and tortoise. They are seen not only in the lower part, as Engelmann stated, but also in the upper part. The ganglia vary greatly in size, containing from 1 to over 100 cells. Rud. Maier made an exhaustive investigation of the nervous system of the urinary tract. He used several animals as well as the human being for his study. He states that ganglia of different sizes exist in the mucosa, the muscle layer and the outer fibrous coat throughout the whole course of the urinary canal. And in the ureteral wall he found nerve plexuses with ganglion cells in the outer fibrous and mucous coats. The muscle layer also has nerve fibers and ganglia, especially between the outer longitudinal and the circular coats. Timofejew and Smirnoff also mentioned many ganglia in the lower part of the ureter.

Protopopow found nerve branches to the middle part of the ureter besides those from the plexuses renalis, vesicalis and spermaticus. They are very fine, starting from the inferior mesenteric ganglion and running up to the ureter in an ascending or descending direction. He described a nerve plexus and ganglion cells in the outer fibrous and muscle coat. In the mucosa of the frog and

rabbit he demonstrated nerve fibers but none of ganglionic structure. In making histological preparations I employed fresh and macerated ureters of pig, dog, cat and man. The maceration was done with 25 per cent acetic acid solution acting for two weeks to two months. The material was dissected into separated layers under the binocular microscope and examined before and after staining with picric acid, picrocarmin and gold chloride.

The following method was used as a special stain for ganglion cells.

1. Fix for twenty-four hours in the mixture of Mueller fluid, 90 cc.; glacial acetic acid, 10 cc.; mix just before using.
2. Wash in 70 per cent alcohol until colorless.
3. Stain entire piece in alum carmin cochineal over night: Powdered cochineal, 60 grams; ammonia alum, 60 grams; mix and boil in 800 cc. distilled water for twenty minutes, filter, add small crystal of thymol to prevent mould.
4. Put in 80 per cent alcohol and dissect under the binocular microscope at any time.

One can get very satisfactory results by staining nervous elements *intra vitam* with methylene blue by Ehrlich's method. Michailow's modification of this method, as described below, gave useful results. A small amount of methylene blue was dissolved in a Locke's solution made according to the formula recommended by Roth:

Locke's solution no. 2 (without sugar)

Sodium chloride.....	9.0 grams
Calcium chloride.....	0.24 gram
Potassium chloride.....	0.42 gram
Sodium bicarbonate.....	0.1 gram
Distilled water.....	1000 cc.

For the purpose of shortening the time for staining, I oxygenated this methylene blue solution for five minutes.

One-half to two hours after killing animals by bleeding, the ureter was removed carefully and dissected into layers under the binocular microscope. Small pieces of folded filter paper soaked

in the methylene blue solution, prepared as above, were spread inside a watch-glass leaving a small vacant place in the center. A small piece of a dissected layer of the ureter was placed, so that the tissue was covered. This preparation was examined under the microscope at a temperature of 38°C.

A few minutes after the stain was added, the nerve fibers together with the cells began to take up the stain and they reached a point of maximum absorption after twenty to thirty minutes. Permanent preparations were made as follows:

1. Fix for twenty-four to thirty-six hours in a mixture of molybdate of ammonium, 4 grams; distilled water, 100 cc.; hydrochloric acid (concentrated), 4 drops.

2. Wash thoroughly in distilled water for twenty-four hours.

3. Alcohol in increasing concentration, xylol and balsam.

In preparations made with these several methods I found nerve fibers and ganglion cells in the entire course of the ureter from the renal pelvis to the bladder end. The outer fibrous coat and mucosa (or more specially the submucosa) are the important layers as regards the nerve system of this organ. In the muscle layer there can be seen a few nerves, which seem to have no functional relationship with the muscle fibers themselves but appear to connect the outer and inner nerve systems.

1. In the outer fibrous coat

In the outer fibrous coat nerve trunks which approach the ureter ramify entering its wall symmetrically and these branches connect with one another to make an unbroken network, as if the ureter were wrapped by a nervous mesh. The nerve fibers show marked difference in size at several levels of the organ. Generally both ends have some well developed nerve trunks, which give off a number of branches. At the lower end especially there can be observed macroscopically a very strong plexus consisting of big nerve fibers with ganglia. This can be noticed most clearly in the cat's ureter. On the other hand nerve fibers in the middle portion are more uniform in size than those at the ends.

The network of the nerve fibers has quite large, rhomboid meshes, which are placed parallel to the ureteral axis, and grow thicker toward the inner side, making a well developed network between the outer fibrous and the muscle layers. Some of these nerve fibers enter apparently in between the outer longitudinal muscle fibers. They are composed of medullated fibers, chiefly, with some of the non-medullated variety.

At the points of division or sometimes in the course of the nerve fibers there are found many ganglia in the coat. The number of the ganglion cells varies within wide limits. The simple ganglia are composed of only one or a few cells, the medium ones contain 10 to 50 cells and the large ganglia over 100 cells. A very large ganglion containing about 130 cells was found in the lower part of the cat's ureter (plate 2, figs. 13 and 14). There were numerous variations in the situation and structure of the ganglia so that they had markedly different types, as is true generally in the case of the peripheral ganglion.

Generally large ganglia containing over 100 cells are found only in the lower part of the ureter. In the middle and the upper parts there are smaller ganglia containing 30 cells at the most. The ganglia in the middle part especially are the smallest in size and for the most part contain few or even a single cell.

2. In the mucous coat

Nerve fibers in this coat become markedly thinner and more uniform, so that most of them comprise only a few nerve fibrils. They make a fine network with small meshes, which are relatively ovoid or round in shape (plate 2, fig. 8). The nervous system in this coat grows thicker toward the muscle layer, so that the network is developed mostly in the outer side of the submucosa between the latter and the muscle layer. The submucosa, therefore, contains the main nerve supply of the ureter. The nerve fibers are mostly non-medullated.

Many ganglia which contain a single cell or a few cells can be seen in the nerve fibers. The ganglia also have various situations in relation to the nerve fibers.

A majority of the multicellular ganglia have the form of a ball apparently penetrated by a nerve fiber (plate 2, fig. 11).

There are numerous varieties in the form of the cells, some being spindle-shaped, others triangular and still others square, or exhibiting numerous modifications from polygonal to round. The size also varies within certain limits, some being four or more times larger than the epithelial cells, while some smaller ones are of the same size as the cells in the sheath of the nerve fibers. By the method of vital staining with methylene blue only the fine granulations in the protoplasm of the nerve cells are stained a strong dark blue, so that there can be seen no exact contour of the cells. In the center or sometimes in the periphery of these granulations one brighter area remains, which indicates the nucleus. On the other hand the cells in the nerve sheath are more purple in color and are stained homogeneously with the nucleus a little stronger. The majority of the ganglion cells have their own processes, which may be one (unipolar) or two (bipolar), or sometimes more (multipolar). A few of them have no processes (apolar), the cell being connected with the nerve trunk by connective tissue fibers which resemble a true process (pseudopolar) (plate 2, fig. 14, *b, m, a*).

The cell body itself shows a homogeneous protoplasm and has granulations in it (plate 2, fig. 9, *gc*). A few cells have rather gross granulations surrounding especially their nucleus, which can be observed clearly in vital staining with methylene blue. There is only one nucleus which is large in size and faint in color (plate 2, fig. 9, *n*). It has a honeycomb-like structure with one to five nucleoli (plate 2, fig. 9, *nl*).

In the structure of the ganglia I could find nothing resembling the glia in the brain as Rud. Maier described. Homogeneous substance between the several nerve cells seen in some of my preparations were considered rather to be cross-sections of small parts of nerve cells cut at their periphery, as was demonstrated after careful examination of serial sections.

3. In the muscle layer

The nerve elements in this coat are usually very scanty. There can be found a number of nerve fibers uniform in size but of much greater thickness than those of the mucosa. The majority of them can be followed obliquely, as if they penetrated the muscle layer to make connection between the two plexuses in the outer fibrous and inner mucous coats. I could not find very fine nerve fibrils ending between muscle fibers as Engelmann mentioned. They seem to me, therefore, to be connecting nerve fibers of the two plexuses, rather than a functional nerve supply to this coat, because the nerve fibers are too small in number compared with the amount of the muscle fibers. The nerve fibers are mixed medullated and non-medullated. No ganglia were found in this coat. In some separated pieces of the muscular coat there may be noticed ganglionic structures (ganglia or single cell), but they are situated always on the surface of the pieces, and belong to the adjacent fibrous or mucous coats. Although the muscle layer is supplied poorly with nerves, it is wrapped by two unbroken nerve networks with many inclusive ganglia on both the outer and inner sides, which constitute the conductor of nervous impulse to the muscle tissue.

CONCLUSIONS

1. The outer fibrous coat is an important seat of nerves and blood vessels.

a. Nerve trunks, which enter this coat at several points, starting from the plexuses renalis, vesicalis and spermaticus, as well as from the inferior mesenteric and other ganglia, make numerous divisions successively connecting with each other to make a plexus with long and rhomboidlike meshes. This plexus is developed mostly on the deeper side between the fibrous and the muscle layer.

b. At the intersections of this plexus or in the course of the nerve fibers there are found ganglia of different sizes containing from 1 to over 100 ganglion cells.

2. Muscular layer:

a. Takes up half or more of the thickness of the ureteral wall and varies in thickness at different levels.

b. In regard to the course of the muscle fibers there is a marked difference at different points.

i. In the upper end the muscle fibers make a braided membrane, taking their course in all possible directions.

ii. The isthmus has a more regular arrangement showing inner longitudinal and outer circular layers.

iii. In the remaining part of the upper third the layer formation is distinct, so that toward the lower end there are three definite layers—outer and inner longitudinal and middle circular.

iv. The middle part has a well developed muscle coat of three definite layers, especially a strong circular band made up of thick bundles. Toward the bladder the circular layer decreases gradually, while the two longitudinal coats increase proportionally.

v. In the lower third the longitudinal muscle fibers appear in much greater quantity than the circular fibers and at the lower end of the ureter, not including the intraparietal section, the circular fibers make a broken circle in between the longitudinal fibers, the latter playing the chief rôle in the formation of the muscle coat.

vi. Immediately after entering into the bladder wall the ureter loses the circular fibers leaving only a longitudinal layer, which also a short distance beyond, disappears on the medial side of the ureter. The longitudinal fibers on the outer side of the ureter, however, can be followed to the level of its orifice.

c. There is no definite sphincter at the lower end, although certain structures form a mechanism to prevent a reflux of the bladder content.

d. The muscle layer has a small amount of nerve fibers of uniform size. No ganglionic structure exists in this coat, but it is wrapped closely on both sides by two well developed nerve plexuses, which probably innervate the muscular layer.

3. In the mucous coat especially in the submucosa:

a. The nerve fibers are thin and build a fine network with relatively round meshes. Single nerve cells or ganglia contain-

ing a few cells are found in this network in large numbers. The nerve plexus is developed mostly between this layer and the muscle coat.

b. In this coat there are found neither definite mucous glands nor goblet-cells, which seem to produce a secretion.

c. In the normal condition diffuse lymphoid tissue or sometimes well developed nodules are found almost constantly in the coat in greater or less amount.

4. Ganglia and nerve cells vary very much in size and form, large ganglia being observed only in the outer fibrous coat, while smaller ones exist in both the outer fibrous and mucous coats. Nerve cells have one, two or more processes, which can be followed for a distance as non-medullated nerve fibers. Some of the ganglion cells have no processes.

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PLATE 1

FIG. 1. The upper end of the pig's ureter, stained with hematoxylin and eosin. $\times 14$. Only one layer of a braided membrane of muscle fibers. Muscle fibers also are cut in relatively short stretches and placed parallel with each other.

FIG. 2. The isthmus of the pig's ureter, stained with hematoxylin and eosin. $\times 14$. Muscle bundles become longer. This fact indicates that their course becomes more transverse. Inner longitudinal (*il*) and circular coat (*c*) appear distinctly.

FIG. 3. The middle part of the pig's ureter, stained with hematoxylin and eosin. $\times 14$. Muscle bundles are bound in large bundles and become thicker especially in the circular coat (*c*). Inner and outer longitudinal coats (*il* and *el*) appear, so that there can be seen three definite layers. Lymph nodules (*lym*).

FIG. 4. The lower end of the human ureter except the intraparietal section, stained with hematoxylin and eosin. $\times 14$. Almost all fibers of the muscle layer run longitudinally (*l*). There is no difference between the outer and inner longitudinal coats. Circular muscle fibers are scattered in between (*c*). Waldeyer's ureter sheath (*w*) can be distinguished from the proper muscles of the ureter. Between these two a few of relatively large blood-vessels are noticed (*bv*).

FIG. 5. The upper part of the intraparietal part of the human ureter, stained with hematoxylin and eosin. $\times 14$. There remains only one longitudinal layer of muscle, whose bundles are thick and large in number (*l*). Waldeyer's sheath becomes distinct and massive (*w*). There are observed a number of relatively large blood-vessels between the latter and the muscle layer. A part of the bladder muscles can be seen in this section (*bl*).

FIG. 6. The middle part of the intraparietal part of the human ureter, stained with hematoxylin and eosin. $\times 14$. Muscle layer disappears in the medial side, making half circle in the lateral side (*l*). Bladder muscles grow in mass (*bl*).

FIG. 7. The lower part of the intraparietal part of the human ureter, stained with Van Gieson's method. $\times 14$. A few of the muscle bundles are scattered in between connective tissue on the outer side (*l*).



Fig. 1

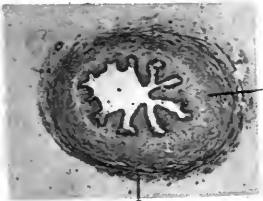


Fig. 2

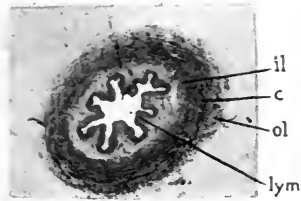


Fig. 3

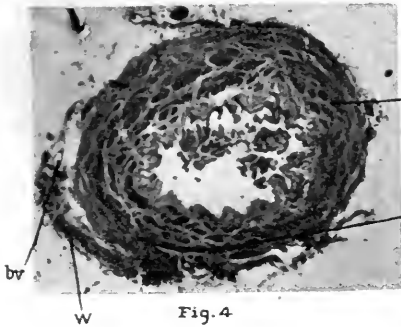


Fig. 4

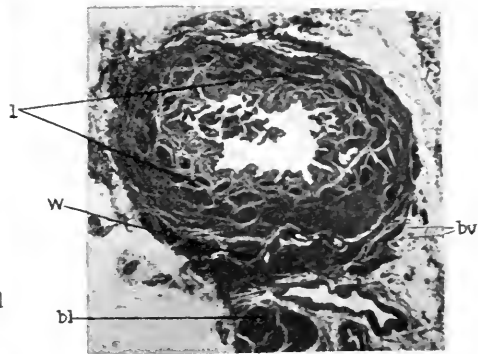


Fig. 5

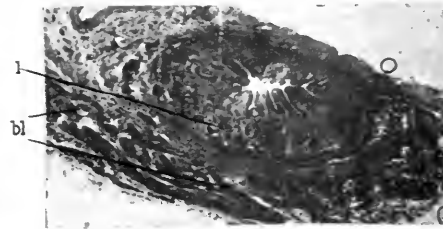


Fig. 6

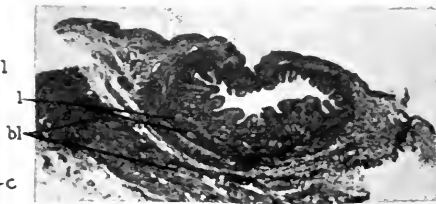


Fig. 7

PLATE 2

FIG. 8. Nerve plexus in the submucosa of the dog's ureter, stained with methylene blue in vitum. $\times 60$.

FIG. 9. Ganglion in the outer fibrous coat of the human ureter, stained by hematoxylin and eosin. $\times 280$. Five cells (*gc*) are contained within a sheath (*cap*). The ganglion cells have one nucleus in each (*n*), in which there can be seen a distinct nucleolus (*nl*). This ganglion is placed on one side of a large nerve trunk (*nt*).

FIG. 10. An isolated ganglion cell in the nerve trunk of the outer fibrous coat of the human ureter, stained with hematoxylin and eosin. Ganglion cell (*gc*). Nerve trunk (*nt*). $\times 280$.

FIG. 11. Ganglion in the submucosa of the pig's ureter, stained by cochineal carmin after dissecting out. $\times 60$. Ganglion (*g*). Nerve fiber (*nf*).

FIG. 12. Large ganglion in the outer fibrous coat of the cat's ureter, stained by cochineal carmin. This ganglion contains over 100 cells. $\times 60$.

FIG. 13. Ganglion in the outer fibrous coat of the cat's ureter, stained by hematoxylin and eosin after making section. $\times 280$. Cells vary very much in size and form, and in the number of processes.

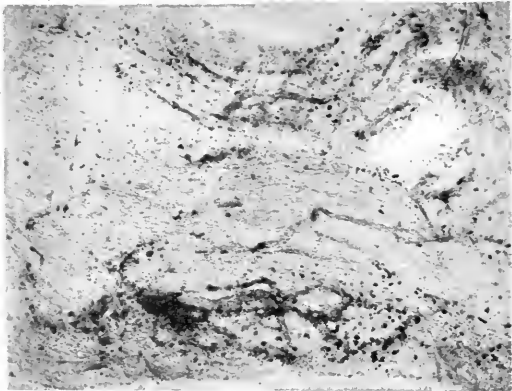


Fig. 8

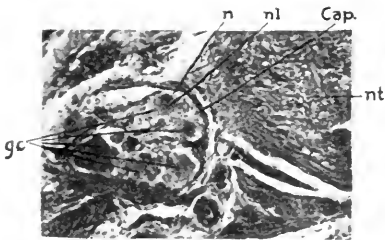


Fig. 9

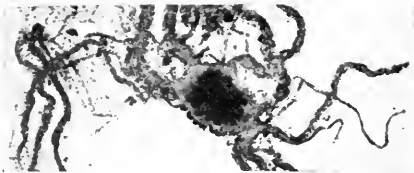


Fig. 12

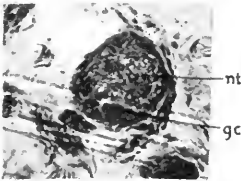


Fig. 10

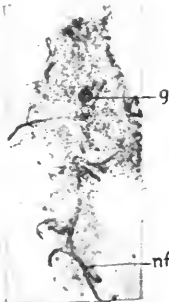


Fig. 11

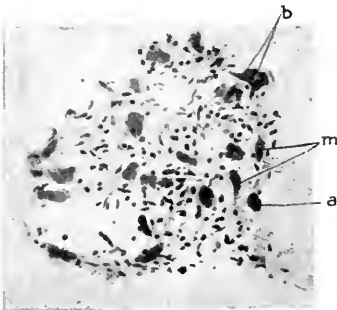


Fig. 13

THE COLLICULUS SEMINALIS AT BIRTH—WITH A REPORT OF THE ORIGIN, DEVELOPMENT AND ZONAL DISTRIBUTION OF ITS GLAND TUBULES¹

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A full appreciation of the nature and extent of the pathology of the posterior urethra can be attained only after a thorough understanding of its normal structure. Most urethral lesions originally located or later progressing posteriorly beyond the triangular ligament involve to a greater or lesser degree the colliculus seminalis. This is particularly true of most urethral infections. Among other lesions we occasionally encounter cysts, polyps and a motley array of congestions, hyperemias and irregularities which we are wont to treat somewhat empirically, it is true, in an effort to alleviate certain sexual symptoms. Bearing in mind the clinical importance of these pictures an effort has been made to establish more definitely our knowledge regarding the morphology and structural content of the human verumontanum.

The basis for this communication was obtained from the study in serial sections of the colliculus seminalis and adjacent posterior urethra of a male infant at birth. The specimen, imbedded in paraffin, was cut in sections 40 micra thick. These were stained in the usual manner in haematoxylin and eosin and every section from the internal or vesical sphincter down to the membranous urethra was studied separately. In addition, four reconstructed drawings were made from these sections. each magnified fifty times to insure greater accuracy, to graphically represent

¹ Read before the Section on Urology of the American Medical Association, at the Seventieth Annual Session, Atlantic City, June, 1919.

the number, form, position and arrangement of the inherent glandular elements present at this time.

Proceeding anteriorly from the point of bladder closure the first indication of the collicular elevation is encountered a few sections beyond the last vestige of the internal sphincter in the form of the beginning superior striae. These narrow ridges or folds, three in number, continue down the urethra, gradually

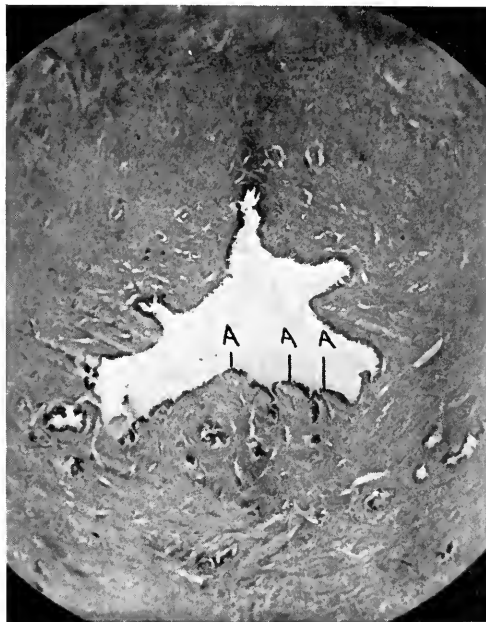


FIG. 1. CROSS SECTION THROUGH THE POSTERIOR PORTION OF THE PROSTATIC URETHRA

A A A, the three superior striae (fetus at birth)

increasing in height until the three become fused into a mid-urethral prominence which is the superior or upper portion of the true colliculus. These striae are made up of a few strands of connective tissue and a portion of the urethral wall itself while their covering is composed of mucous membrane several layers deep similar in all respects to the mucosa lining the sides and roof of the urethra. The basement membrane is readily

identified beneath the mucosa following each ridge like elevation in its entirety. The striae measure 0.3 mm. in length and the middle one is larger than its fellows on either side. At the union of the three superior striae the verumontanum measures 0.1 mm. in height. From this point it continues in an upward curved direction gradually increasing in height and breadth until at the

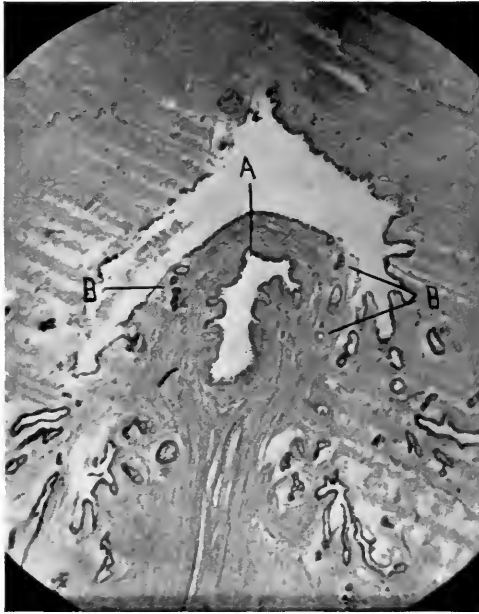


FIG. 2. CROSS SECTION THROUGH THE UPPER PORTION OF THE VERUMONTANUM

A, Prostatic utricle; B, gland tubules of mucous membrane origin (fetus at birth).

point of greatest dimensions it measures 4 mm. long, 1 mm. high and 1.5 mm. wide. It is made up at this time of the prostatic utricle, which opens at its summit into the urethra and on either side the ejaculatory ducts which likewise open into the urethra. In addition there is contained within its substance a myriad of tubular nests which at first glance seem to possess no definite position or arrangement. These tubules are supported

by a definite intertubular stroma which in the peripheral portion becomes more dense and assumes the rôle of a definite capsule.

After a careful study of the origin and distribution of the tubular content of the verumontanum, it has been possible to classify its inherent glandular elements in three groups as follows: (1) those of mucous membrane origin, (2) those of

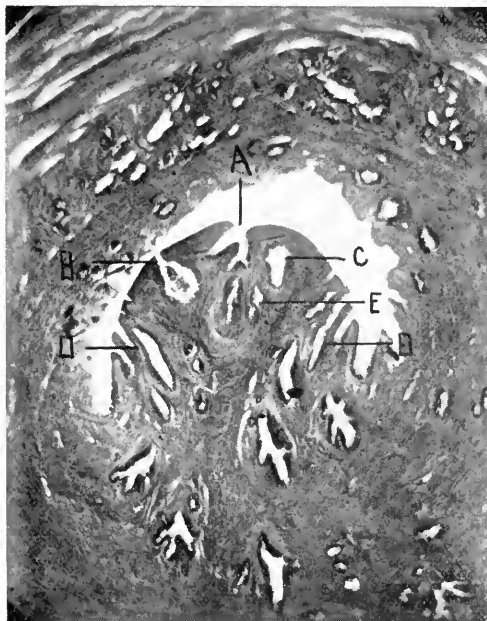


FIG. 3. CROSS SECTION THROUGH THE MIDDLE PORTION OF THE VERUMONTANUM

A, Prostatic utricle opening into the urethra; B, opening of the left ejaculatory duct; C, right ejaculatory duct; D, tubules of prostatic origin; E, gland tubules of utricular origin (fetus at birth).

prostatic origin, and (3) those arising from the sinus pocularis or prostatic utricle.

The first of these, the tubules of mucous membrane origin, occupy a position in the upper third of the organ or that portion lying nearer the internal vesical sphincter. These are found immediately beneath the union of the superior striae and continue their course through the verumontanum until they reach

a point at about the middle of the extent of the prostatic utricle. They assume, for the most part, a position parallel to the urethral floor with their blind ends pointing backward toward the bladder. They all open very definitely into the prostatic urethra through the sides and top of the verumontanum. In addition to being found in the superior third of the structure they are all

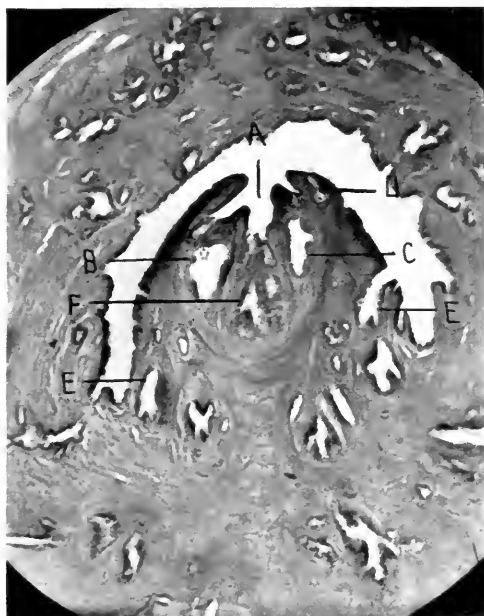


FIG. 4. CROSS SECTION THROUGH THE MIDDLE PORTION OF THE VERUMONTANUM

A, Prostatic utricle opening into the urethra; B, left ejaculatory duct; C, right ejaculatory duct; D, tubules of mucous membrane origin; E, tubules of prostatic origin; F, tubules of utricular origin, some opening into the utricle (fetus at birth).

located during their entire course very near the surface or in other words in the peripheral zone of the organ. In size they vary considerably, but as a group they are slightly larger than the tubules arising from the sinus pocularis yet do not assume the proportions attained by the tubules of prostatic origin. In the graphic reconstruction of this area it has been possible to

identify thirteen tubules on one side of the upper third of the verumontanum which number comprises about one-half of the total tubules of mucous membrane origin existing in this specimen at birth (fig. 7).

The second group of tubules, those of prostatic origin (from the sub-urethral portion of the middle lobe) occupy a position in what is approximately the middle third of the organ. In-

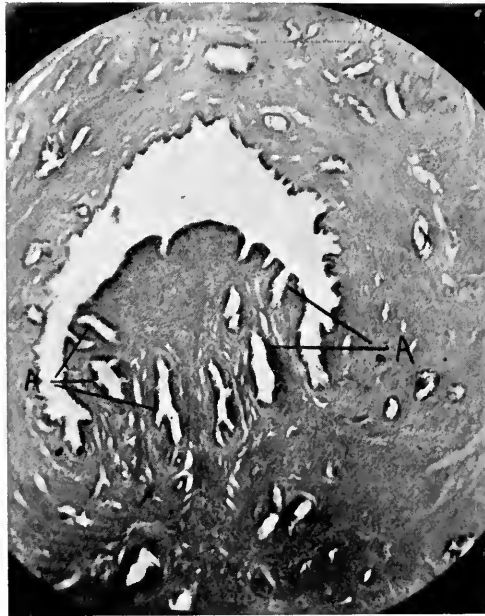


FIG. 5. CROSS SECTION THROUGH THE LOWER THIRD OF THE VERUMONTANUM

A, tubules of prostatic origin (fetus at birth)

dividually these tubules are larger than those of either of the other two groups and extend for the most part in a perpendicular direction. Their blind ends are situated well within the deeper substance of the verumontanum yet all pursue an unrestricted course upward to open along the sides of this structure. A few, however, open along the mid line and when the latter occurrence takes place their orifices are usually found anterior or in

front of the openings of the utricule and ejaculatory ducts. This tubular group is notably deeper in location than the preceding and its area of distribution is more extensive. Compared with the first mentioned series the tubules of prostatic origin may be said to be confined to the sub-peripheral zone of the collicular substance. These tubules extend farther anteriorly than any of the others and as a whole their walls together with the lumen of each tubule is less given to bizarre irregularities than those of the other two groups. In the reconstructed chart of this group it has been possible to identify in one-half of the verumontanum fourteen tubules of unmistakable prostatic origin. From this

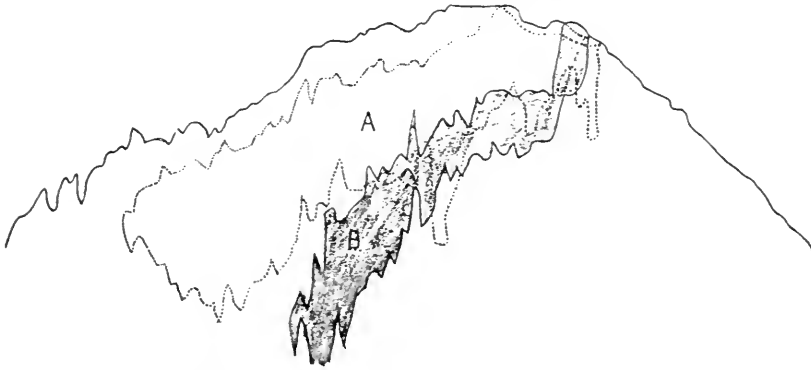


FIG. 6. OUTLINE OF VERUMONTANUM RECONSTRUCTED FROM 126 SERIAL SECTIONS

A, Prostatic utricule; B, right ejaculatory duct (fetus at birth)

number we can legitimately ascribe an approximate total of twenty-eight tubules of prostatic origin entering into the content of the organ at birth (fig. 8).

The third and last group of essential collicular tubules comprises those having their origin from the sinus pocularis or prostatic utricule. These are formed from the evagination of the walls of the utricule and histologically are similar to those of the two groups described above. Individually these are the smallest of the tubules contained within the verumontanum and at the same time their walls and lumina present the most irregularities. Their course in the verumontanum is strikingly horizontal

and they assume a longitudinal axis practically parallel to the floor of the urethra. Their blind ends are directed backward toward the internal vesical sphincter, while every one, as would naturally be expected, opens into the cavity of the prostatic utricle. It is interesting to note in this connection that no tubules either of mucous membrane or of prostatic origin have been observed opening into the utricle. The location of these utricular glands is confined for the most part to the most anterior portion of the utricle, with only a few short scattered tubules situated along its middle portion, while the posterior third of the utricle is entirely free from any glandular elements opening



FIG. 7. OUTLINE OF VERUMONTANUM RECONSTRUCTED FROM 126 SERIAL SECTIONS

A, Prostatic utricle; B, right ejaculatory duct; C, gland tubules of mucous membrane origin (fetus at birth).

therein. The most anterior tubules of this group are located beneath the utricle and in the midline while only a few are observed located and opening along the sides of the organ. From their area of distribution in relation to the others described, this group may be termed the middle zone tubules of the verumontanum.

The number of primary utricular tubules encountered in the reconstruction of this area was fourteen for one-half of the structure. This, however, included all of those opening in the midline which fact would permit us to ascribe not more than

about twenty tubules of this type comprising the total of the third group (fig. 9). The lower or most anterior third of the verumontanum in the specimen studied at birth is entirely free from any tubular elements. It is made up only of stroma similar in all respects to that found in other portions of the organ. The verumontanum terminates in three rather ill defined ridges, the inferior striae, which decrease in size as they traverse the prostatic urethra and finally are lost by becoming part and parcel of the urethral floor.

In a more detailed study (2) has been reported the origin and development of the verumontanum from Müller's tubercle, a

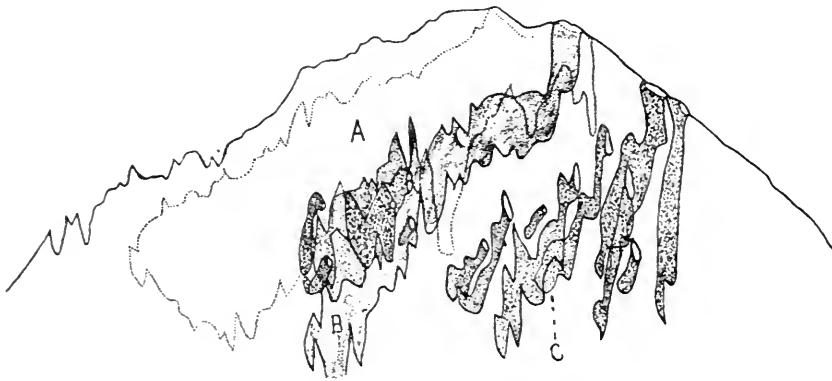


FIG. 8. OUTLINE OF VERUMONTANUM RECONSTRUCTED FROM 126 SERIAL SECTIONS

A, Prostatic utricle; B, right ejaculatory duct; C, gland tubules of prostatic origin (fetus at birth).

rounded elevation situated on the mid-ventral floor of the urogenital sinus. This prominence is formed by the upward pushing of the two Wolffian ducts to open into the urethra, augmented by the three superior striae. At the thirteenth week of fetal life the verumontanum exists as a simple rounded elevation on the floor of the prostatic urethra. It is formed by the upward growth of the ejaculatory ducts and contains at this time in addition to the above mentioned structures the prostatic utricle, a closed sac like cavity. The mucosa covering the verumon-

tanum is smooth with no evidence of pitting. A mass of undifferentiated mesenchymatous cells comprises the main body of the organ and nowhere is there to be found any tubular elements.

By the fourteenth week the first gland tubules are encountered. These are of mucous membrane origin and arise from the increased activity of its epithelial covering by a process of invagination into the peripheral portions of the upper third of the organ. At this period no other tubules are found, the sub-peripheral and middle zone strata being clearly undifferentiated mesenchyme. These tubules are all superficial in location and lined with epithelium continuous with that covering the veru-

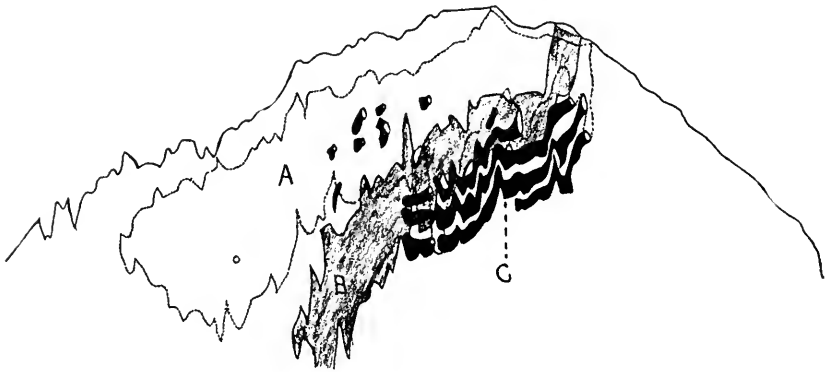


FIG. 9. OUTLINE OF VERUMONTANUM RECONSTRUCTED FROM 126 SERIAL SECTIONS

A, Prostatic utricle; B, right ejaculatory duct; C, gland tubules of utricular origin (fetus at birth).

montanum. All degrees of epithelial evagination are demonstrated at this time from a simple pitting of the mucosa to true tubule formation.

The second group of glandular elements, those of prostatic origin, are recognized by the sixteenth week of fetal life. These tubules arise from the sub-urethral portion of the middle lobe of the prostate. In the study of numerous sections it has been possible to identify these structures first in the prostatic region and to follow them to their final position in the verumontanum.

The upward slanting course of the ejaculatory ducts apparently is a factor of considerable importance in pushing these tubules upward toward the collicular prominence. The tubules of this group occupy a position along the middle third of the verumontanum. Also they are situated deeper than those of mucous membrane origin and fill in what may be termed the sub-peripheral zone. All of these open directly into the posterior urethra along the sides of the verumontanum.

The picture presented at the nineteenth week of intra-uterine life offers no material change from that just described except that the tubules of prostatic origin are more numerous.

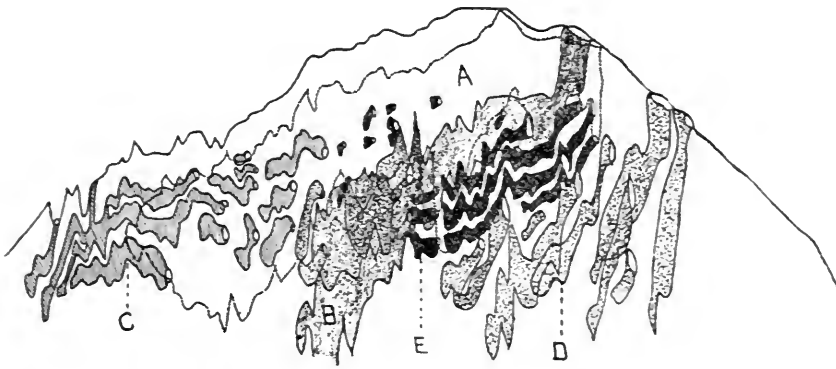


FIG. 10. COMPOSITE DRAWING RECONSTRUCTED FROM 126 SERIAL SECTIONS SHOWING THE ENTIRE GLANDULAR CONTENT OF THE VERUMONTANUM

A, Prostatic utricle; B, right ejaculatory duct; C, gland tubules of mucous membrane origin; D, gland tubules of prostatic origin; E, gland tubules of utricular origin (fetus at birth).

By the twenty-fifth week the tubules of utricular origin appear. These have their origin from an evagination of the walls of the prostatic utricle and are situated for the most part at the anterior portion of the utricle. A few however, are scattered along the sides of the cavity and one very definite group lies beneath the utricular sac. From their location in the center of the verumontanum this group is termed the middle zone tubules.

At the thirty-first week the prostatic utricle has opened into the

urethra. The three groups of true collicular tubules can now be readily identified in their respective zones of distribution. Those of mucous membrane and those of prostatic origin open entirely into the prostatic urethra along the sides and top of the verumontanum while those of utricular origin open into the prostatic utricle. All of the glandular elements are now supported by a well formed inter-tubular stroma not unlike that found in the prostate gland itself. Between the thirty-first week of intra-uterine life and birth there occurs no striking morphological changes other than a continued growth of the structures already present.

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A SIMPLE APPARATUS FOR CONTINUOUS AND AUTOMATIC BLADDER IRRIGATION¹

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From the therapeutic standpoint a continuous antiseptic lavage of the bladder will be more efficient than an intermittent one. This is one of the well established lessons of the war in the treatment of infected wounds. It is what we hope to have some day as an internal urinary antiseptic.

In the treatment of cystitis² without residual, periodic catheterization with lavage and instillations is usually preferred to a retention catheter, or urethro-vesical irrigations without the use of a catheter may give better results. But there are some types in which irritability is so great that the patient quickly becomes worn out from the almost continuous desire or need to urinate. In these cases a retention catheter may give relief but requires almost constant care and repeated irrigations and instillations in order to accomplish therapeutic betterment. With the well-to-do patient a sufficient force of nurses is available for these bladder treatments but the proper care of ward patients by this method is almost hopeless.

The following apparatus³ which can be quickly fitted up in any hospital has been found of value during the past two years in the care and treatment of a certain limited number of bladder cases.

¹ Model exhibited in April, 1918, at California State Medical Meeting, Del Monte, California.

² Cystitis in the vast majority of cases is secondary to a renal or ureteral lesion, to an urethral, prostatic or seminal vesical abnormality or to some disturbance of the bladder itself such as stone, tumor or diverticulum. Recognition and relief of any of these primary foci will almost invariably result in a cure of the cystitis without treatment.

³ In Guy's Hospital Gazette, 1917, xxi, 211, an apparatus of similar principle is described by Lever. The apparatus described in this paper was in use a year before this.

The apparatus depends upon hydraulic suction as illustrated in figure 1. It consists in practice of a series of three rubber tubes leading to a glass Y-tube connection to a retention catheter in the bladder (see fig. 2). The irrigation solution drips from a large elevated basin, 1, through a Murphy drip tube 2, into the bladder, 4. The outflow follows another tube, 5, held up near its end above the level of the bladder in a loop, 6, so that the dependent end hangs lower than the bladder and tubular system. The third tube, 8, leads to a glass burette, 9, and acts as an air-vent. The amount of bladder distention is regulated by the height of the loop at 6, which, together with the length of 7, influences the degree of suction with each period of overflow. The air vent, 9, cuts off the full force of the column of fluid, in 7, and prevents a painful pull on the bladder. The tip of the glass tube or burette should be drawn out to a small hole so that filling and emptying will be slow and gradual. This is also important in securing complete syphonage of the bladder. The drip tube, 2, allows a visual regulation of the inflow which according to its rate and depending on bladder conditions and the height of the suction loop, 6, can be made to automatically trip the suction from every fifteen minutes to two hours. Should the irrigation can, 1, run dry the apparatus will not function until disconnected at 4, and the tubes have been refilled and cleared of air.

Contrary to the belief generally held that bladder irrigations are contraindicated in the treatment of vesical tuberculosis this method has been used in four post-operative cases with gratifying relief to the patients and apparent improvement of the ulcerations. It is not applicable in the care of prostatics as bladder drainage is not complete with it. Suitable cases for its use suggest themselves from the limitations already indicated.

The following are brief abstracts of a few cases of vesical tuberculosis treated by the above method:

Case I Age, thirty-three; male. Admitted January 4, 1918. One or two months previous to entrance, the patient developed frequency, no pain or aches, and this symptom increased. On May 8, 1917, a

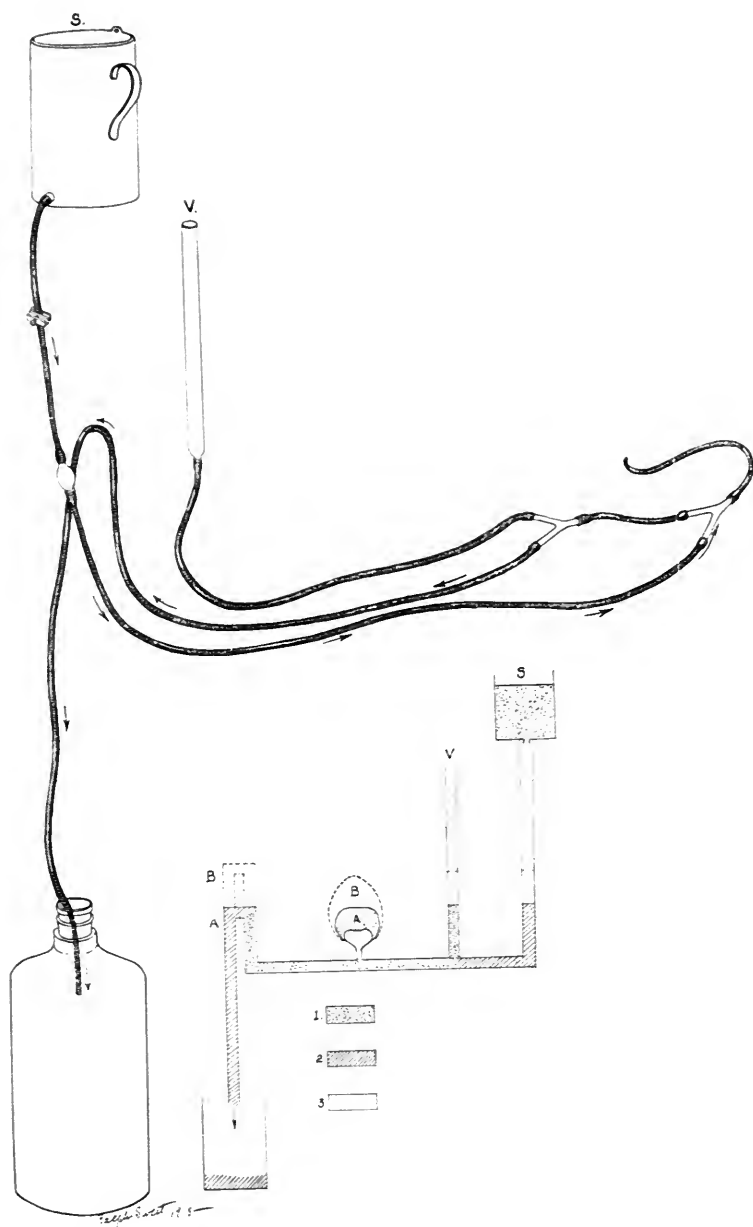


FIG. 1. DIAGRAMMATIC REPRESENTATION OF THE PRINCIPLE INVOLVED IN THE CONTINUOUS AND AUTOMATIC IRRIGATION APPARATUS

1. Represents system filled to height A. The bladder distends to a pressure equal to the weight of column of fluid in ascending loop of the syphon A, which is also the same in V. As this pressure increases by inflow from S, the column of fluid will pass over into the descending limb of the loop and empty the system by suction.

2. Represents the system emptied. V has a small outlet so that it fills slowly and empties slowly. When empty air enters and prevents a painful pull on the bladder.

3. Represents a greater distention of the bladder produced by raising the height of the syphon to B.

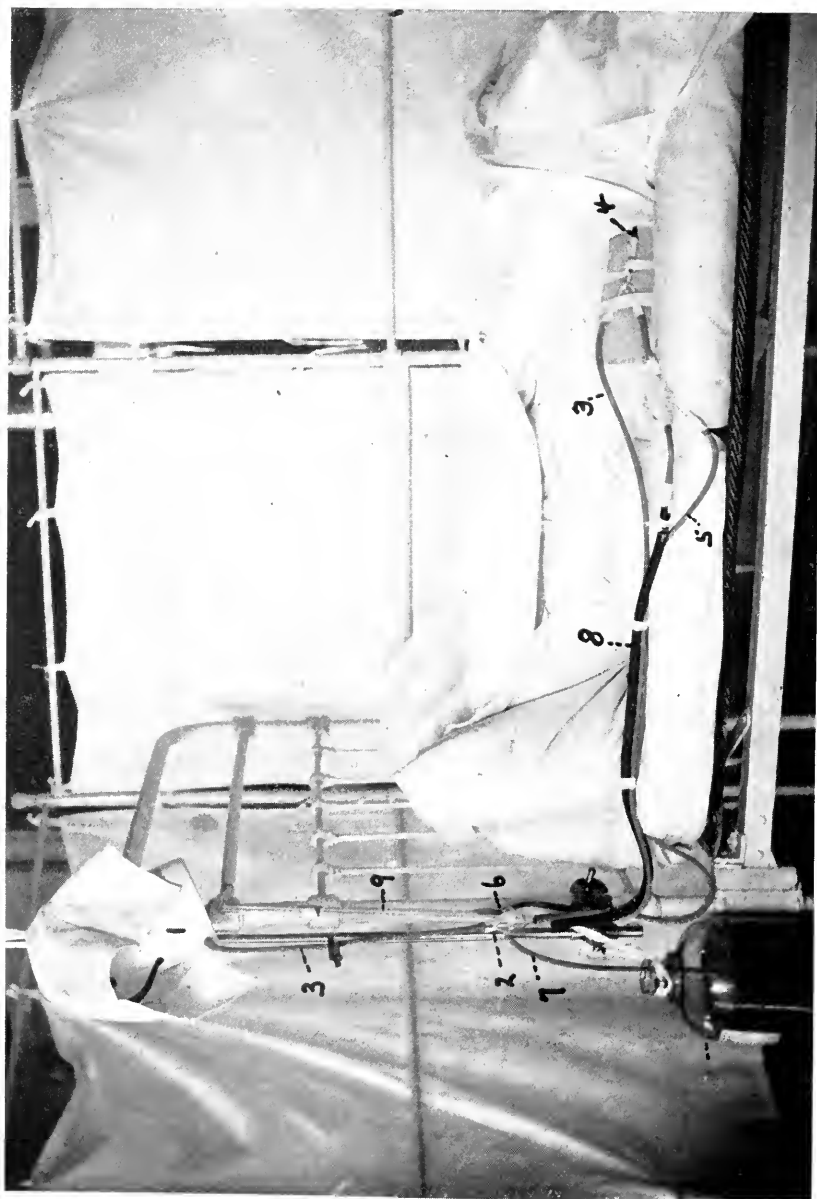


FIG. 2. APPARATUS IN USE AT UNIVERSITY HOSPITAL IN CASE I

1. Irrigation can. We have alternated according to the type of infection and the degree of vesical irritability; boric acid, 4 per cent; potassium permanganate, 1-12,000 to 1-4000; bichloride of mercury, 1-100,000 to 1-60,000; phenol, 1-100 to 1-60; silver nitrate, 1-20,000 to 1-6000.
2. Murphy drip tube by which the inflow may be regulated (usually 15 to 40 drops per minute).
3. Inflow tube to
4. Catheter in bladder
5. Outflow tube to
6. Suction loop emptying by
7. Long end into waste bottle
- 8 and 9. Air vent which is drawn out to caliber of 0.5 to 1 mm. diameter at end



FIG. 3. APPARATUS QUICKLY ASSEMBLED FOR USE IN A TUBERCULAR BLADDER
IN A CASE AT ST. LUKE'S HOSPITAL

Nephrectomy two years previously. Innumerable vesical ulcers present. Tenesmus and frequency pronounced. Irrigator used continuously for three weeks with comfort and complete relief. Patient writes from Sacramento a year later that he is still perfectly well.

diagnosis of tuberculous left kidney was made. On June 8, 1917, nephrectomy was performed. The frequency was relieved for about one month and then started again, becoming progressively worse up to time of entrance. There has been hematuria since onset of symptoms at various intervals. No acute retention. *P. E.* Practically negative. Blood pressure, 130-90. Urine showed a trace of albumin, no sugar, numerous epithelial cells, many pus cells and the predominating organism was a chain of short bacilli, a few staphylococci and a few long light-staining granular bacilli. Following the intramuscular injection of phenolsulphonphthalein 48 per cent was recovered in two hours. January 19, cystoscopy and fulguration of several tuberculous ulcers of the bladder. January 21, continuous irrigation was started through a retention catheter but patient could stand very little pressure at this time and could endure the continuous irrigation for a very short period. January 23, continuous irrigation again established working nicely all day and was run through the night of the 24th without any discomfort. The patient was able to stand more pressure. January 25, cystoscopy. The ulcer on the fundus which had been fulgurated at the last treatment appeared as a burned blackened area and the neighborhood was reddened, granular and still somewhat papular but no other signs of ulceration were seen. February 1, continuous irrigation which had been kept going since January 25 with complete comfort was discontinued. The patient still had some discomfort in the bladder so on February 4 the continuous irrigation was again started using 1-90,000 bichloride of mercury for four hours. February 5, patient was irrigated with 1-2000 bichloride for twenty to thirty minutes due to nurse's error and upon complaining of burning in the bladder, the solution was investigated and the error found. The bladder was then immediately irrigated with boric and then egg albumin, and the continuous irrigation with boric solution again established. The bladder was somewhat tender for a few days but no further symptoms developed. February 11, patient was cystoscoped and cystoscopy showed the bladder healed except for one very small ulceration on the fundus. Patient received irrigations at night followed by an enfumage in the morning of iodoform vapor and was allowed to be up and around during the day. February 21, another cystoscopy and fulguration of the small tubercle were performed. February 22, patient discharged. The bladder was practically healed and patient was no longer troubled with frequency, burning or any urinary symptoms. He has been seen several times since leaving the

hospital and is suffering no discomfort and has no longer any frequency or burning on urination.

Case II. Age, twenty-two. Admitted February 17, 1918. This patient was sent to American Lake training camp by the Draft Board in October, 1917, and here his symptoms which had been very mild previously were greatly exaggerated and he was placed in the hospital where a diagnosis of tuberculous left kidney with a tuberculous bladder was made. At the time of his admission to the University Hospital, he was voiding every two hours during the day and four to five times during night. The urine was blood stained and there was a great deal of burning and urgency with each urination. A diagnosis was made of tuberculous left kidney with tuberculous cystitis. February 26, nephrectomy was performed. Patient's recovery was good although he still complained of the bladder symptoms. March 15, continuous irrigation started and on the first day patient could stand it only for a few hours, 1-10,000 potassium permanganate solution being used. However, the next day the bladder felt much better and continuous irrigation was again started using 1-10,000 potassium permanganate for six hours, boric acid for two hours, phenol 1-100 for one hour, boric acid for three hours, bichloride 1-80,000 for six hours followed by boric acid. Patient was able to retain continuous irrigation until about 9 o'clock that night, and that night slept much better than any time since onset of symptoms. The continuous irrigation was again started the next day and repeated for three days. Patient, however, was not able to retain catheter during the night. Patient was discharged on March 20 with his frequency practically gone and no longer any burning on urination. The urine was also free of blood cells. Patient has not been heard from since discharge from hospital.

CONGENITAL OBSTRUCTION OF THE POSTERIOR URETHRA¹

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An obstruction more or less complete, due to the presence of abnormal valves or folds in the posterior urethra has occasionally been described in the literature. The condition has always been regarded as one of great rarity. The great majority of the cases has been recognized only at autopsy, the diagnosis made during life having had no relation to the lower urinary tract. On reviewing the records of The Johns Hopkins Hospital, twelve cases not previously reported have been found, in which the diagnosis has been confirmed by instrumental methods, operation or autopsy. It seems probable, therefore, that the condition is considerably more frequent than would be inferred from the attention given it in the past.

The earliest mention of the condition found in the literature is in the work of Langenbeck on Lithotomy, published in 1802. Thirty years elapsed before the subject was again referred to by Velpeau (1832), who described several anatomical specimens in which there were present in the posterior urethra valve-like folds which he felt might be of clinical importance. Tolmatschew, in 1870, was the first to give a comprehensive discussion of the subject and recognized the condition as a pathological entity. But these were all chance autopsy findings and it was not until 1912 that the first clinical diagnosis of valvular obstruction of the posterior urethra was made, this case being operated by one of us at this hospital. This and three other similar cases were reported before the Johns Hopkins Medical Society in November, 1913.

¹ Read at the meeting of the Association of Genito-Urinary Surgeons at Atlantic City, New Jersey, June, 1919.

Since then the development of the X-ray and renal function tests has made possible more accurate diagnosis before operation. In one of our cases (no. 5), the X-ray was used to confirm the diagnosis and to locate more accurately the point of obstruction. An operation was successfully carried out. This case was reported before the Johns Hopkins Medical Society in November, 1913. Another patient (no. 9) came to the hospital for the cure of a second degree hypospadias. The alarmingly low renal function as determined by phenolsulphonphthalein suggested a further investigation which resulted in the diagnosis of congenital obstruction of the posterior urethra which was confirmed later at operation.

THE CONDITION AS A CLINICAL ENTITY

Etiology. An inquiry into the etiology of any congenital defect naturally suggests an investigation of the embryologic development of the part in question as well as a study of the anatomical variations, which may occur within normal limits. It is interesting therefore in reviewing the literature of the subject to find explanations based upon these two possibilities. Thus Tolmatschew (23) whose article appeared in 1870 and who was the first to investigate carefully the pathology of the condition placed great importance upon the folds and ridges which are normally present in the urethra and explained the enlarged folds by assuming them to be simply overgrowths of these anatomical structures. Lindeman (8), in 1904, and Wilckens (11), in 1910, both inclined to this same view. Englisch has also recognized the frequent occurrence of folds arising from the anterior and posterior aspects of the verumontanum which are normally present and only assume a pathological rôle when they reach a height sufficient to obstruct the outflow of the urine. This view was apparently generally accepted until the appearance of Bazy's (17) article in 1903 in which he contended that the urogenital membrane of the embryo would occupy in the later stages of development a position corresponding to the most frequent site of the valves in question. He believed therefore that these valves were in reality a persistence of this membrane. Thompson

(10), in 1907, accepted this view and amplified it somewhat, likening the valves to an imperforate hymen or persistent anal membrane. Lederer (14), in 1911, and Knox and Sprunt (13) in 1912 also inclined to the embryological explanation of these structures. More recently Lowsley (7) has advanced a view based upon his studies of the embryology of the prostate and microscopic examination of his specimen of congenital obstruction. While agreeing with neither of the foregoing opinions, his explanation has points of similarity with both. He feels that the condition is an anomaly of the Wolffian and Müllerian ducts. He says:

These structures, which in the male become the ejaculatory ducts and the utriculus prostaticus, enter the prostate near its base and course in an oblique direction through that organ until they approach the urethra, at which point they turn and for a short distance run parallel with its axis, finally opening into its lumen. During their passage through the prostate their musculature is bound together by a very definite, firm sheath of connective tissue. On their approach to the urethra they push the floor of that structure up into a mound forming the verumontanum and still are separate from all other structures, their tissues being superimposed upon those of the urethra. Ordinarily, immediately below the openings of the ejaculatory ducts and utricle, the tissues surrounding them become distributed among the fibers on the floor of the urethra. Thus the verumontanum gradually becomes smaller and smaller until just below the apex of the prostate it disappears completely, spreading out laterally in the form of little bands which disappear on the floor or walls of the urethra. In the specimen under consideration, although a number of fibers are disposed in the usual manner, the majority of them continue downward on the floor of the urethra. At the point where the verumontanum usually disappears, these fibers attach themselves to the entire circumference of the urethra, with the exception of a small portion of the floor to the left of the median line, thus producing an almost complete blocking of the urinary passage.

In our opinion none of the views outlined above adequately explains the development of *all* the types of obstruction reported. It is possible that the explanation suggested by Lowsley may account for certain of the varieties of valve-formation found

below the level of the verumontanum, particularly those arising from the bifurcation of the ridge which originates from the anterior aspect of this structure. To us a far more probable explanation is suggested by an illustration in a recent article by Watson (28) entitled "The Structure of the Verumontanum." This is a photograph of a transverse section through the urethra

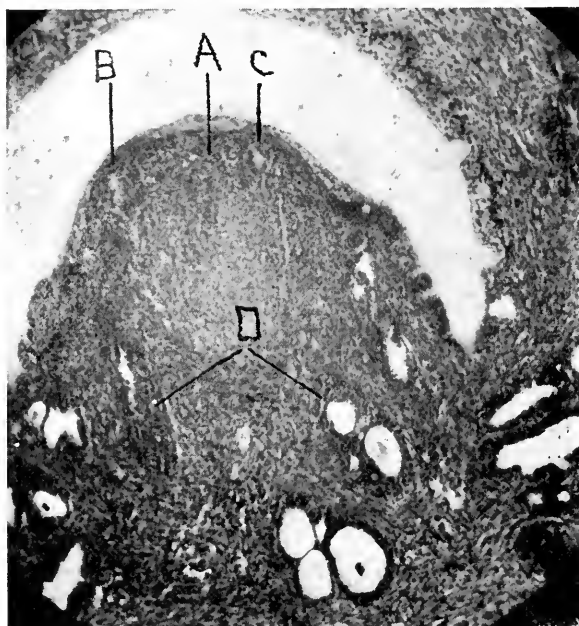


FIG. 1. TRANSVERSE SECTION THROUGH VERUMONTANUM OF SIXTEEN WEEKS' OLD FETUS

Showing normal relations of verumontanum to the roof of the urethra. From article by Watson, The structure of the verumontanum, *Jour. Urology*, ii, October, 1918.

at this level in a 14 weeks' old fetus. Arising from the summit of the verumontanum are three fibrous strands which are attached to the roof of the urethra. It seems highly probable that this anomaly represents an early stage of this type of valvular obstruction. This anomaly, however, seems wholly inadequate in accounting for the origin of the valve-like obstruction at the vesical neck which arises from the bifurcation of the ridge which

springs from the upper aspect of the verumontanum, as well as the semicircular folds in the roof or the floor which may occur at any level. The anatomical view advanced by Tolmatschew may explain the former variety while the embryological explanation suggested by Bazy appeals to us as very probably accounting for the occurrence of the semicircular diaphragms which



FIG. 2. TRANSVERSE SECTION OF VERUMONTANUM OF 14 WEEKS' OLD FETUS

Showing fibrous strands connecting tip of verumontanum with roof of urethra. From article by Watson, The structure of the verumontanum, *Jour. Urol.*, ii, October, 1918.

are attached to the urethra throughout half of its circumference and the iris-like variety of Jarjavay.

An analysis of the cases of congenital obstruction which are available for study shows that the majority come under observation during infancy or early childhood. Thus, of 34 cases, in which the age is noted, 12 were under one year; 9 from one to five years; 4 from five to ten years; making a total of 25 under ten

years as against 9 above that age. The earliest case is that of Fuchs who noted the condition in a five months' fetus, while the eldest, a man of eighty-five years, was reported by Iverson.

PATHOLOGY

It seems fitting in this connection to consider first the types of congenital obstruction of the posterior urethra. In 5 of our cases

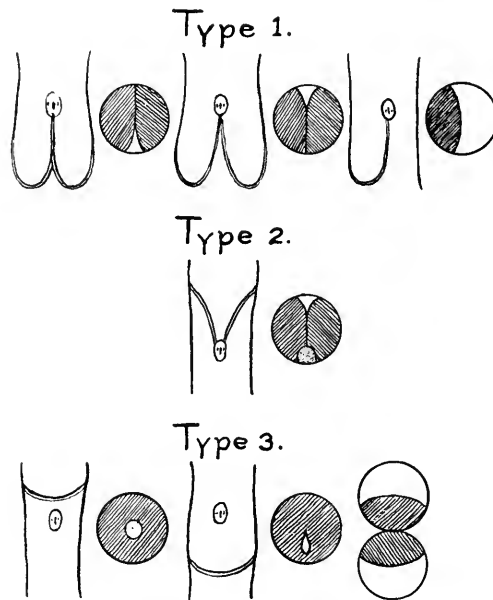


FIG. 3. DIAGRAMMATIC SKETCH SHOWING VARIATIONS OF THE THREE TYPES OF CONGENITAL OBSTRUCTION OF THE POSTERIOR URETHRA

a study of the anomaly was made post mortem, while in 7 others the condition was recognized during life, although in only 3 of these cases was any accurate information obtained regarding the exact type of the obstruction by instrumental examination. A study of the cases reported in the literature proves quite definitely that three general types of valve formations exist.

Type I. In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like



FIG. 4. ENLARGED PHOTOGRAPH OF DRAWING FROM ARTICLE BY KNOX AND SPRUNT
(See Amer. Jour. Dis. Child., lx, 1912.) Showing more in detail the situation
and nature of the valvular obstruction. See case 15.

processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets, directed upward and forward which may be attached to the urethra throughout its entire circumference. In the majority of cases of this general type the fusion of the valves anteriorly is not complete, there existing at this point a slight separation of the folds. However, in a few of the cases of which Lowsley's and



FIG. 5. ENLARGEMENT OF LOWER PORTION OF FIGURE 8

The obstruction shown is a variation of the type which is usually bilateral and springs from the bifurcation of the crista urethralis (type 1).

Knox's and Sprunt's are examples, the anterior fusion is complete while a cleft exists between the folds posteriorly. Another subdivision which really belongs to this general type consists of but a single instead of a double valve.

Type II. In the second general type of which we have one example, there occurs a more or less cylindrical ridge similar to that found in the preceding type with the exception that it passes

from the upper aspect of the verumontanum toward the internal sphincter where it divides into two fork-like processes which are continued as membranous sheets which are attached to the urethra just outside the internal sphincter in a manner similar to that described in the foregoing type.

Type III. There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum as the types just considered. This was first mentioned by Jarjavay who described it as an iris valve because of the similarity in shape to the iris of the eye. This obstruction was attached to the entire circumference of the urethra, there being a small opening in the center. Incomplete varieties of this type have been described, the most common being a more or less crescentic or semicircular

TABLE 1
Type of obstruction

TYPE	OUR CASES	CASES FROM LITERATURE	TOTAL
I	5	14	16
II	1	0	1
III	3	6	9

fold crossing the urethra and being attached either to the roof or floor.

The grouping of the cases according to this classification is indicated in table 1. In two of our cured cases and in the two from the literature the exact type was not determined, while in two other cases from the literature classification is impossible.

It should be borne in mind that varying degrees of congenital obstruction may exist, which may result in symptoms so slight that the condition is unrecognized. The occurrence of infection not infrequently results in a marked increase of obstruction in these cases, symptoms of the condition dating from this time. The recognition of a congenital obstruction late in life in an individual giving the history of only slight obstructive symptoms till a short time before, is most readily explained on this basis. It seems probable furthermore that even in the absence of

infection the obstruction in many of these milder cases may increase by the development of pockets or shallow diverticula behind the partially obstructing valves.

An interesting feature of these types of urethral obstruction concerns the arrangement of the folds which frequently offer little or no impediment to the passage of fluid or instruments from without inward but which reduces greatly the calibre of the urethra during urination. The concave surfaces of the valves are always directed toward the bladder and are ballooned out by the urinary stream. It should be noted in this connection, however, that except in those cases where only slight obstruction exists that the valves are continually ballooned out, at least when the patient is in an erect posture. In practically all cases in which the obstruction to urination is at all marked, the urethra above and the internal sphincter are greatly dilated, in consequence of which, the urethra behind the obstruction is always more or less urine filled.

The changes in the urethra above the valve differ very little from those resulting from any urethral stenosis except that they are frequently more pronounced because of the long duration and degree of the obstruction. There is always more or less dilatation of the urethra and internal sphincter and in certain of the cases a marked hypertrophy of the longitudinal urethral musculature is evidenced by cord-like bands passing from the point of obstruction to the bladder. In cases of long standing obstruction, shallow diverticula may be present in the prostatic furrows and the ejaculatory ducts and utricle may be widely dilated. These changes have been quite prominent in two of our cases.

The bladder invariably shows a marked grade of hypertrophy which may be present with or without dilatation. The variation in the bladder capacity depends apparently upon several factors. It has been noted, for instance, in the infants of our own series, as well as in several cases reported that the bladder capacity varies inversely as the degree of hydroureter and hydronephrosis. In other words in the cases in which the kidneys and ureters communicated with the bladder cavity by large orifices, the bladder was usually contracted. In the beginning of the obstruction,

however, the degree of vesical dilatation may have been marked but a free communication with a dilated upper urinary tract would explain on mechanical grounds the small hypertrophied bladder. In no case in our series and in none of the reported cases coming to our notice have vesical diverticula been found.

The changes in the ureters and kidneys warrant only brief mention as they differ in no particular from those resulting from any urinary obstruction of long standing. Extreme grades of hydroureter are seen frequently, the ureters approaching or exceeding the intestines in size. Corresponding changes are likewise noted in the kidneys. It is interesting to note that the degree of dilatation of the ureters and kidneys is rarely uniform on the two sides. In the literature as well as in our own cases, the left ureter and kidney very frequently showed the greater dilatation.

Symptomatology. That the symptoms of congenital obstruction of the urethra have not been clearly recognized is evident from the large percentage of cases in which the true condition has been unsuspected until autopsy. Yet the symptom complex is after all reasonably clean cut. Systematically considered the symptoms may be classed under four heads:—

a. Local symptoms due directly to the obstruction. These are incontinence, dysuria and retention. The incontinence frequently dates back to birth, the story being that the child has always urinated every half hour or so, or has dribbled urine constantly. This incontinence is often combined with crises of retention lasting many hours. Retention may occur alternately with incontinence, or it may be an outstanding symptom. In Bednar's case for example, the infant passed no urine for the five days he was under observation before death.

b. Symptoms resulting from dilatation of bladder, ureters and kidneys. By far the most common complaint in these cases is "distended abdomen." It is present in practically all of the carefully observed cases. The dilatation of the urinary organs causes discomfort, which may amount during periods of retention to very severe pain. Dyspnea is common from the increased intra-abdominal pressure.

c. Symptoms resulting from renal destruction. These are those of chronic diffuse nephritis. The patient may show edema, though this is not an early or a constant finding in infancy or early childhood. Anemia is usually present. Diarrhea and vomiting may be so prominent that the case is regarded for a time as a primary intestinal disturbance. These intestinal symptoms are certainly of toxic origin. In one of our cases acidosis was marked, probably the result of renal insufficiency. Uremia as a terminal picture was present in several of the cases.

d. Symptoms due to infection. Sooner or later most of these patients develop an infection of the urinary tract. It is interesting to note that in several of the cases the underlying obstruction was first recognized when there was superimposed upon it an infection. Those patients with infection show as a result of it pallor, anorexia, loss of weight and strength and fever which is apt to fluctuate rapidly and is frequently accompanied by chills. It is furthermore to the infection that the leucocytosis in these cases must be attributed.

To summarize, the symptoms are those of a local obstruction in the urethra combined with the consequent symptoms of urinary back pressure and infection.

In but few of the cases reported have the symptoms been clearly indicated. However, grouping such as are given (see table 2) shows that some disturbance of urination has been most frequent. Where vomiting, abdominal distention, and loss of weight have been prominent, the patient has been in infancy or early childhood.

Diagnosis. A review of the literature of congenital obstruction of the posterior urethra discloses but two cases in which a confirmed diagnosis was made during life. So far as we are aware, with these exceptions all of the reported cases have been discovered post mortem. This fact is quite surprising in view of the comparative frequency of the condition, the invariable history of obstructive symptoms since birth and the ease of diagnosis by the application of modern methods. It seems advisable, therefore, to consider the following points in diagnosis.

a. The history. A careful clinical history is the first indispensable step to correct diagnosis. The symptoms which are more or less characteristic of those resulting from obstruction to the outflow of urine will be somewhat modified by the degree of that obstruction and the age of the patient. In infants and very young children with severe grades of obstruction, incontinence of urine is a very common symptom, the incontinence being naturally the paradoxical variety. In many of these cases the history of abdominal tumor resulting from a distended bladder or hydronephrotic kidney may be elicited from the parent. In the less severe grades of obstruction hesitancy, the passage of a small,

TABLE 2
Symptoms

	OUR CASES	CASES FROM THE LITERA- TURE	TOTAL
Abdominal distention.....	2	3	5
Vomiting.....	3	1	4
Loss of weight.....	2	2	4
Urinary			
Difficulty.....	4	6	10
Pain.....	4	2	6
Incontinence.....	1	4	5
Retention.....	3	1	4
Frequency.....	3	0	3
Pyuria.....	1	1	2
Hematuria.....	0	2	2

weak stream, diurnal frequency of urination and nocturnal enuresis are commonly met with. Indeed, the presence of any symptoms suggesting urinary obstruction in a male child or young adult, particularly when the urine is uninfected, should immediately call attention to the possibility of some congenital urethral defect.

b. Abdominal palpation. The changes in the bladder and upper urinary tract resulting from urethral obstruction are demonstrable in many of these cases by abdominal palpation. In the more marked types of obstruction, particularly in those cases having incontinence, the bladder can frequently be

felt as a hard, conical or pear shaped tumor, extending as high as the umbilicus. In one case reported a diagnosis of sarcoma was made. In this type of case it is possible frequently to palpate the ureter as a large doughy mass extending from the bladder to the costal margin in which region an hydronephrosis is frequently palpable. Owing to the emaciated condition of many of these patients, abdominal palpation is greatly simplified and frequently furnishes the examiner with very valuable data.

c. Instrumental examination. The use of the cystoscope and urethroscope is naturally quite limited because of the fact that the majority of these cases when first seen are either infants or very young children. A small catheter, however, can usually be passed and an obstruction occasionally demonstrated in the region of the external sphincter. In the majority of these cases, however, little or no difficulty is encountered in passing a catheter but the ease of instrumentation is by no means an index of the degree of urinary obstruction. As indicated above, many, if not the majority, of these cases exert a valve action which operates from within outward, the valve flaps being ballooned out during the passage of urine or forming pockets in which the instrument may lodge if retrograde catheterization is attempted during operation. In very young infants a no. 5 or 6 ureteral catheter may be employed, a fine wire stylet considerably facilitating its introduction in difficult cases. Residual urine in variable amounts is recovered by the catheter. We have been able in some cases in which there was considerable destruction of the upper urinary tract to obtain a rough idea of the degree of hydroureter and hydronephrosis. With the patient in the prone position the catheter is passed into the bladder, its complete emptying being facilitated by gentle pressure over the suprapubic region. This urine is carefully measured and the amount of bladder residual recorded. Pressure is now made over one kidney and ureter, the amount of urine recovered from the catheter roughly estimating the capacity of this ureter and kidney. Pressure is finally made over the second kidney and ureter, and the output determined in a similar manner.

Cystoscopy furnishes little information regarding the type of urethral anomaly. The presence of residual urine, trabeculation, diverticula and dilated ureteral orifices, however, is proof positive of vesical obstruction. Dilatation of the internal vesical sphincter and prostatic urethra to the point of obstruction is also usually demonstrable. The use of the urethroscope or better still, the cysto-urethroscope, as it permits of urethral irrigation, enables one to obtain an excellent view of the obstruction in certain cases. It was possible in one of our cases to demonstrate without question its valve-like character. The changes incident to urethral obstruction are frequently demonstrable in the urethra above the point of narrowing. Thus, in our cases more or less dilatation was noted and in certain instances of long standing obstruction pouch formation may be found in the prostatic furrows and a widening of the diameter of the ejaculatory ducts and utricle.

Cysto-uretero-pyelography furnishes a far more accurate means of determining the degree of destruction of the upper urinary tract and is also valuable in determining the point of obstruction in young children in whom cystoscopy and urethroscopy are impossible. In many of the cases with hydroureter and hydronephrosis, the ureteral orifices are widely dilated and fluid introduced into the bladder passes into the kidney without difficulty. Thus in one of our cases where fluid was introduced into the bladder filling it to its capacity the patient complained of no sense of discomfort suprapubically, his symptoms being referred to the region of the kidneys. It is thus possible in many cases to secure valuable information by means of the X-ray. After the urinary tract has been emptied as completely as possible, 10 per cent thorium citrate or some other suitable medium is introduced through the catheter by gravity and the X-ray taken. Satisfactory filling of the upper urinary tract is frequently facilitated by having the patient in a moderate Trendelenburg position. This procedure can be carried out with perfect safety and much of the discomfort following the introduction of the thorium obviated by syphoning it off and irrigating with plain water.



FIG. 6. ENLARGEMENT OF THE LOWER PORTION OF FIGURE 9

Showing the dilatation of the internal sphincter and urethra to the point of obstruction.

Table 3 gives the more important clinical observations with the frequency of their occurrence. The case records are frequently lacking in this respect, so that the data is far from complete.

Preliminary treatment. As many of these cases present marked grades of renal destruction, the renal function should be determined in each case and, in the event of marked renal impairment, a preliminary treatment not unlike that carried out in prostatic obstruction should be instituted immediately. This is particularly indicated in case a suprapubic or perineal operation is contemplated. Catheter drainage of the bladder and the forcing of fluids is followed invariably by marked improvement in the

TABLE 3
Clinical findings

	OUR CASES	CASES FROM THE LITERA- TURE	TOTAL
Distended bladder.....	5	11	16
Residual urine.....	7	1	8
Reduced renal function.....	6		6
Pyuria.....	7	4	11
Obstruction to catheter.....	6	5	11
Urethroscope shows obstruction.....	3		3
X-ray shows obstruction.....	2		2

renal function and the operative risk is greatly diminished. In all cases in which a retention catheter is employed, scrupulous care regarding antisepsis should be observed. Frequent bladder irrigations and the introduction of 10 per cent argyrol through the catheter will prove very helpful. During the course of the preliminary treatment, the improvement in renal function is best followed by means of phenolsulphonphthalein. These tests should be carried out at least twice weekly. Not infrequently in these cases, as is true in any type of urinary retention, the renal function may be lowered temporarily following the institution of catheter drainage. It will gradually improve, however, finally reaching a level beyond which it will not pass. When this highest level is reached and the percentage output of phenolsulphon-

phthalein is constant as shown by repeated tests, operation may usually be safely carried out, irrespective of the degree of renal destruction.

Treatment. In the surgical treatment of congenital obstructions of the posterior urethra, three avenues of approach immediately suggest themselves. The selection of the method to be employed in a given case will vary somewhat with the age of the patient and the personal preference of the operator.

1. *Intraurethral procedures.* In the removal of congenital obstructions of the posterior urethra, several methods are available. For convenience of description they may be divided into (a) instrumental; (b) urethroscopic; (c) excision with Young punch instrument.

a. *Instrumental.* In certain cases, an obstruction in the posterior urethra is encountered on attempting to introduce an instrument into the bladder. Particularly is this true in those cases in which the fusion of two valves is almost complete. It may be possible in certain cases to remove the obstruction by forcibly passing a metal instrument through it. This plan of attack has been carried out successfully in two of Bazy's cases by means of a sound, while in one of our cases it was accomplished with a straight urethroscope. In other cases a filiform may be introduced after which the passage of followers of large size may result in the destruction of the valve. In certain others it may be advisable to divide the obstruction with a Maissonneuve urethrotome to be followed by high urethral dilatations.

b. *Urethroscopic methods.* This plan of attack is necessarily limited as in a relatively small proportion of cases is satisfactory urethroscopy possible. In cases in which the urethroscope can be passed, it may be possible to divide or remove the valve more or less completely with suitable scissors. The disposition of the valve, however, may make this procedure impossible in which case its free edge may be grasped by a urethral rongeur and forcibly torn from its attachment. The obstruction may also be destroyed by fulguration in certain cases. The difficulty of the methods just outlined is at once apparent when it is recalled that upon the passage of the instrument the valves may be

pushed aside so that they lie against the urethral walls. These difficulties can usually be overcome by the following procedure:—

c. Excision with Young punch instrument. The technique we have employed in two of our cases successfully treated by this means is as follows: The bladder is first filled to its capacity after which the “punch” is introduced. The obturator is now removed and the instrument slowly withdrawn. The dilated condition of the urethra above the point of obstruction will permit a certain amount of fluid to pass by the instrument thus inflating the valve which will be caught in the fenestra. The knife is now introduced and the obstruction excised. In case the obstruction is bilateral as is frequently the case a second cut may be made. The ease and certainty of this method will be greatly facilitated by a previous knowledge of the position and character of the obstruction, but as most of these cases are children this method is not often applicable.

2. Suprapubic operations. The treatment of these cases through a suprapubic cystotomy can usually be accomplished without difficulty although the method employed may vary somewhat with the position of the obstruction. When this lies above the level of the verumontanum, it may be readily removed by rongeur, scissors or cautery. For those cases in which the valve lies at a lower level, and the most common location for this type is in the region of the external sphincter, its destruction may be accomplished by passing a sound from above downward into the pocket of the valve and forcibly tearing through it. Thus in one of our cases (case 5) in which the valve lay just outside the internal sphincter it was readily destroyed by the electro-cautery. In another case (case 3) located in the mid-prostatic portion the obstruction was readily broken through with the finger. In a third case (case 6) in which the valve occupied the position of the external sphincter its destruction was easily accomplished by a sound, while in another (case 9) the obstruction was removed by means of a rongeur.

3. Perineal method. The patient is placed in an exaggerated lithotomy position and a “seminal vesical tractor” introduced into the posterior urethra which facilitates the exposure of the membranous urethra and the posterior surface of the prostate,

as in conservative perineal prostatectomy. After exposure of the membranous urethra the tractor is carried into the bladder, opened and the prostate is brought down into the field by traction and its posterior surface exposed by pushing back the posterior layer of Denonvilliers fascia and the levator muscle. Incisions are now made through the posterior surface into the urethra on either side of the mid-line, with an inverted V-incision beginning in the region of the apex and taking a slightly divergent course for a short distance above the level of the verumontanum. This triangular flap is then carried back with the floor of the urethra and an excellent view obtained (see plates 1 and 2). If exposure of the urethra between the verumontanum and the bladder is desired, the incisions in the prostate can be carried further toward the internal sphincter. The exposure thus obtained will greatly facilitate the complete removal of the obstruction, following which the prostatic flap is replaced and secured by sutures. A retention catheter is then introduced through the urethra and the perineal wound drained by a single strip of gauze. This operation has been carried out by Young and Geraghty in verumontanitis cases.

Results. The functional results of operation in cases of congenital obstruction of the urethra are very satisfactory but the prognosis in a given case will depend naturally upon the changes in the upper urinary tract subsequent to back pressure and infection. In young children in whom the obstruction is not extreme and the renal damage relatively slight the outlook is most encouraging. In our series extreme grades of renal destruction have been present in all of the adult cases and while operation has been followed by improvement both in renal function and in general health, the ultimate prognosis in these cases is generally bad.

In a small percentage of cases the radical removal of these obstructions will be followed by urinary incontinence, irrespective of the avenues of approach selected. The occurrence of this distressing condition will depend upon the degree of obstruction present but chiefly upon the duration of that obstruction. In other words, it is actually dependent upon the degree

of pressure atrophy of the internal sphincter and urethral musculature. This is invariably more pronounced in adults and the possibility of post-operative incontinence should be very carefully considered in these cases. Thus, in one of our patients, aged twenty-four, in whom removal of the obstruction was carried out with the "punch," the operation was followed by incontinence while in another, aged forty-two, having as severe a grade of obstruction and presenting even greater urethral and sphincteric dilatation back of the stricture, the removal of but one valve was followed by perfect urinary control.

CASE REPORTS

In the following cases the diagnosis of congenital obstruction of the posterior urethra was made before operation, at operation or at autopsy. The case histories are given herewith in the order of age.

Case I. This patient was born February 18, 1916, and when eleven days of age was seen in the Dispensary of the Harriet Lane Home where the examination, save for the fact that he was undersized, was negative. He returned one month later with a complaint of vomiting and it was noted at the time that his abdomen was distended. Upon the next visit the mother reported that the child had not voided for two days. The bladder could be definitely felt as a hard, rounded mass extending half-way to the umbilicus. An unsuccessful attempt was made to pass a catheter. On April 11, 1916, because he was losing weight and seemed quite ill, he was admitted to the hospital. The rib margins flared and a remarkably symmetrical distension of the abdomen, especially in the upper part, was noted. No masses were felt. A rectal tube was passed and some flatus expelled. An X-ray examination, after a bismuth meal, showed a normal gastro-intestinal tract. For five days after admission he seemed to improve, gaining five ounces in weight. On April 17, however, the distension increased, the breathing became labored and an exploratory laparotomy was carried out. A mesenteric cyst was discovered and removed and a cyst of the urachus was left in situ. Following the operation the infant took his feedings badly, so was fed by gavage. The respirations became very deep, suggesting acidosis and 60 cc. of 4 per cent sodium bicarbonate solution

was given into the longitudinal sinus with marked improvement in respiration. The same day the patient was transfused, receiving 45 cc. of the mother's blood. Following this the temperature rose rapidly to 106°; the patient developed convulsions and died.

Autopsy. The bladder was not dilated but its walls were greatly hypertrophied, measuring 9 mm. in thickness. It was moderately trabeculated and the ureteral orifices while not widely dilated were larger than normal. On attempting to pass a probe through the urethra from above downward, an impassable obstruction was met at the prostatico-membranous junction. Upon passing it in the opposite direction, however, no obstruction was encountered. The internal sphincter was widely dilated, measuring 6 mm. in diameter. The anterior wall of the entire urethra was now opened. The prostatic urethra showed considerable dilatation which, however, ended abruptly at its junction with the membranous urethra. The verumontanum was more prominent than normal and springing from its anterior aspect and continuing down the mid-line of the urethral floor, was an hypertrophied ridge which bifurcated at the prostate apex to be continued as membranous folds closely adherent to the urethral wall. These fused in the mid-line anteriorly but a tiny opening was present on the posterior wall (see plate 3). Both kidneys were slightly lobulated, the left soft and fluctuant. The right kidney showed a slight grade of hydronephrosis and the right ureter measured $\frac{3}{4}$ cm. in diameter. The left kidney showed a rather marked hydronephrosis and its ureter was elongated, tortuous and dilated, measuring 1.5 cm. in diameter.

Case II. The patient was brought to The Harriet Lane Dispensary on October 15, 1917, at which time he was three months of age. He was well developed and well nourished and seemed normal physically. He lost weight rapidly, developed a cough, vomited and was admitted to the hospital. The urine showed pus and B. coli. He died soon after admission.

Autopsy. At autopsy the chief points of interest centered about the genito-urinary tract. Both kidneys were slightly enlarged and showed on section slight hydronephrosis. Both ureters were also dilated and tortuous. The bladder was small but its wall was considerably thickened. No obstruction was found at the vesical orifice which appeared to be somewhat dilated. On passing a probe into the urethra from the bladder, an obstruction was encountered in the region of the verumontanum which was passed with some difficulty. No obstruction, however, was evident when the probe was passed in the opposite di-

rection, thus demonstrating the valve-like nature of the obstruction, as is usually seen. The verumontanum was especially prominent, quite firm and hard. The urethra was opened in the mid-line posteriorly but no real valve or stricture was demonstrated. The specimen of this case has been lost and the above notes have been taken from the pathological record. While not conclusively evident of congenital obstruction of the posterior urethra, it seems very probable that this was the actual condition present, and that the specimen, in its removal from the body, was cut off too high up, the obstructing valves remaining behind with the membranous urethra.

Case III. This patient, aged six months, was admitted to the Harriet Lane Home on July 14, 1914. Examination revealed acute otitis media. The patient gave no history of symptoms referable to the bladder but two days after admission it was noticed that the bladder was greatly distended. An attempt at catheterization was unsuccessful because of an obstruction in the region of the external sphincter. Under local anesthesia a suprapubic cystostomy was done. Examination showed considerable dilatation of the prostatic urethra and internal sphincter. Digital palpation revealed a valve-like obstruction stretching across the roof of the mid portion of the prostatic urethra. Very little regarding the character of the obstruction could be learned. The valve was forcibly broken with the finger. The suprapubic wound healed in two months and the patient voided with perfect freedom.

Case IV. This patient, aged fifteen months, was admitted to The Harriet Lane Home on July 30, 1916. His birth was normal and the first six months of his life he did very well. At the age of six months he began to lose weight and vomited frequently. At ten months of age his physician found pus in the urine. On admission, the child was emaciated, under-developed and cried incessantly. The abdomen was soft, the bladder palpable to the umbilicus and the external genitalia normal. The examination of the blood showed a leucocytosis of 20,000 and a hemoglobin of 90 per cent. The urine was infected with the colon bacillus, contained many pus cells and a large amount of albumin. Because of the marked distension of the bladder, a no. 6 ureteral catheter was introduced with some difficulty, withdrawing a large amount of urine. The phenolsulphonphthalein test four days after admission showed an output of 0 per cent the first hour, 5 per cent for the second hour, and during the next six hours, 10 per cent was recovered. During the next two days he became rapidly worse, refused his feedings, developed hyperpnea and projectile vomiting; his temperature rose to 107° and he died.

Autopsy. The findings at autopsy were negative except for the genito-urinary tract. The right kidney was half again as large as normal and showed a moderate grade of hydronephrosis. The ureter was very much elongated, tortuous and measured from 0.5 to 2 cm. in diameter. The left kidney showed a greater degree of destruction, the pelvis was extra renal, quite enlarged and the ureter was about twice the diameter of the right. The bladder was contracted but its wall was markedly hypertrophied, measuring 1.5 cm. in thickness. The vesical orifice was quite dilated, measuring at least 1 cm. in diameter. Below this point the prostatic urethra was dilated to even a greater degree, measuring 2 cm. at its widest portion. On attempting to pass a probe from the bladder downward, an obstruction was encountered 2.5 cm. below the internal sphincter. A probe introduced through the pendulous urethra, however, passed very readily into the bladder without meeting any obstruction. The entire urethra was opened in the mid-line anteriorly, disclosing a remarkable condition. Just at the apex of the prostate and attached to the entire circumference of the urethra in a slightly oblique direction was a fold of tissue, quite thin and fibrous looking. This extended upward from the floor of the urethra for a distance of 4 mm., while on the lateral walls it projected into the urethral lumen for a slightly greater distance. The urethra above the obstruction extended laterally below the upper level of the valve, forming quite pronounced pockets into which the probe undoubtedly lodged when it passed from above downward (see plate 4). The prostatic urethra was quite smooth and nothing resembling the verumontanum was seen. When the urethra was closed a small, oval slit, measuring 3 by 6 mm., existed in the center of the diaphragm.

Case V. Male, aged twenty months, was admitted to the Harriet Lane Home, on August 25, 1913, with the complaint of bladder trouble. The family history was unimportant. He was a full term baby, appeared normal at birth, and did well until five months old, when it was noticed that he had difficulty and pain on voiding. This was attributed to a tight foreskin which was frequently dilated. At ten months he was said to have had typhoid fever. He was ill for five weeks. Following this, as his dysuria persisted, he was circumcised. The wound healed very slowly and the operation brought no relief. His urine at this time was "creamy" and the mother thought that at times there was a discharge of pus on his napkin after which he seemed temporarily free from pain. He had always been constipated and since eleven months of age, he had had frequent vomiting attacks.

Examination showed a pale, fairly well nourished boy with rather flabby musculature. A note made at the time was as follows: "There is a mass continuous with the bladder which extends to the level of the umbilicus. It is conical in shape and freely movable except at the apex. This mass is about 6.5 cm. broad at the base and gradually tapers to a broad, rounded margin above. On the right side, extending from the kidney region to the bladder, is a mass about 2 cm. in diameter. Corresponding to this there is a similar but somewhat smaller structure easily palpable on the left side." Several unsuccessful attempts were made to pass a soft rubber catheter, ranging in size from Nos. 6 to 9 French. In each case the catheter met with an obstruction after passing through the external sphincter. No urine came through the catheter. A filiform was readily passed into the bladder, after which an ureteral catheter could be passed. A large amount of urine was recovered in this way, which showed albumin but no casts. The output of the phenolsulphonphthalein was only a trace in the first two and one-half hours; during the next two hours there was an output of 5 per cent, while during the fifth and sixth hours, 30 per cent was recovered. A thorium cystogram showed a trabeculated bladder with some dilatation of the internal sphincter and adjacent urethra but none of the fluid passed into the ureters.

On October 3, 1913, a suprapubic operation was carried out. The bladder was found to be dilated and hypertrophied. The vesical orifice was quite dilated and just beyond it in the prostatic urethra a small vertical valve-like obstruction could be felt on the left side. This obstructed about one-half of the urethra; was more or less semi-circular in outline and extended from the floor to the roof. It was readily seized with a clamp, pulled into the bladder and destroyed with electro-cautery. Further examination of the urethra showed no obstruction. It was noted at operation that pressure in either flank caused large amounts of urine to escape from the ureteral orifices although these showed no dilatation. The patient was discharged four weeks after operation, voiding with perfect ease. His general health improved rapidly, and he remained well for a year, finally dying of diphtheria.

Case VI. This patient, aged twenty-one months, was brought to the Harriet Lane Dispensary, on August 19, 1913, with an interesting history. He was the first child to be born to the parents alive, there having been three miscarriages. His birth was normal at term. He had been breast-fed for a time, then put on condensed milk. For ten



FIG. 7. CYSTOGRAM OF CASE 5

Showing the dilatation of the vesical orifice and the markedly trabeculated bladder. The obstruction in this case lay in the prostatic urethra just beyond the internal sphincter.

months before admission urination had been painful and periodically (about every two weeks) he had suffered with distension of the bladder. At such times he had been known to go for thirty-six hours without voiding. During his periods of retention he had been unable to sit up because of the pain. After being followed for two months in the dispensary without improvement he was admitted to the hospital.

Examination showed a well developed, fairly well nourished child. His bladder was distended, reaching almost to the umbilicus. Attempts to pass rubber and metal catheters failed because of an obstruction 7 cm. from the meatus. An ureteral catheter was finally passed and 500 cc. of urine recovered. The urine showed no pus but a moderate amount of albumin. The phenolsulphonphthalein test gave an output of 71 per cent the first hour and 10 per cent the second hour.

At operation on November 5 the bladder was opened suprapubically. It was found to be quite dilated and its wall hypertrophied. The vesical neck was widely dilated and the finger was readily passed a considerable distance into the prostatic urethra. When a small sound was passed through the meatus, it met an obstruction in the region of the external sphincter. When the finger was introduced through the vesical orifice the tip of the sound was found to be covered with a thin membrane. Sounds were now passed from the urethra toward the bladder but it was impossible to make the two sounds meet because of the existence of this thin membranous fold. A large probe was bent in the shape of a sound and after some difficulty it was passed from the anterior urethra into the bladder. The condition was believed to be one of congenital obstruction of the urethra and a perineal incision was made into the bulb which appeared to be perfectly normal. The point of obstruction seemed to lie somewhat above the bulb although its exact nature was not determined. The urethra beyond the urethrotomy incision was forcibly dilated with a large sound, thus rupturing the valve. Both suprapubic and perineal wounds healed in one month and the patient left the hospital with no urinary difficulty. He was lost sight of until January, 1919, when he returned to the hospital for a tonsillectomy. He had no urinary symptoms, the urine was perfectly normal and his general condition excellent.

Case VII. This patient, aged two years, was admitted to the Harriet Lane Home on January 25, 1913, for hydrocephalus. During the course of examination it was noted that the urine contained pus and albumin. No history of previous urinary symptoms was obtained. During his stay in the hospital he had periods of complete urinary

retention but was always catheterized with ease, and large amounts of urine recovered. He was last admitted to the hospital in 1916, at which time urinary retention and infection were prominent symptoms. He died on February 3, 1916.

Autopsy. The genito-urinary findings are alone of interest in this connection. The penis, urethra, bladder, ureters and kidneys were

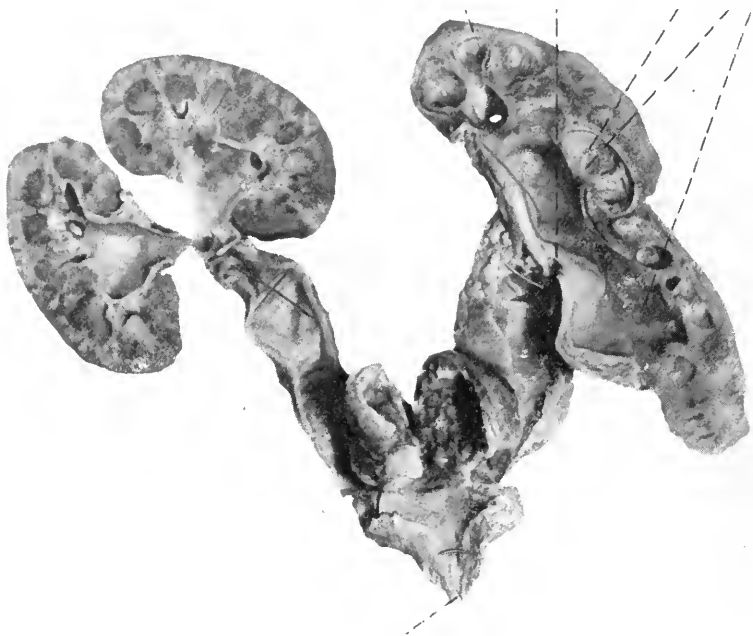


FIG. 8. PHOTOGRAPH OF SPECIMEN FROM CASE 7

Showing dilated posterior urethra, hypertrophied bladder, hydroureters and bilateral hydronephrosis. The valve causing the obstruction is shown on the left wall of the urethra near the point where it is cut off at the end of the dotted line.

removed together. On opening the posterior urethra, a remarkable condition was seen. Beginning at the internal sphincter and extending well below the verumontanum considerable dilatation was noted. From the anterior aspect of the verumontanum an hypertrophied ridge was seen coursing down the mid-line. When the region of the external sphincter was reached, this diverged to the left ending in a thin fibrous fold which was attached to the urethra throughout half of its circum-

ference. The membrane was extremely thin and its concavity directed upward so that it caused apparently considerable obstruction to urination. The bladder was quite small and contracted, and its wall considerably hypertrophied. Both ureteral orifices were only slightly dilated but as soon as they were opened up the ureters were found to be greatly enlarged. The ureteral dilatation was greater on the left, where the circumference of the ureter was 4 cm. throughout its course. The pelvis of this kidney was greatly dilated and its cortex very thin. The right kidney showed a somewhat lesser grade of destruction.

Case VIII. This patient, aged four years, was admitted December 8, 1917, with a history of having had no urinary difficulty until the age of seventeen months. At this time he was operated upon elsewhere for vesical calculi. A suprapubic cystostomy was done but no calculi found. Instead, a diagnosis of vesical papilloma was made and fulgurations were carried out for a time through the suprapubic fistula. Later a portion of the bladder wall was resected and the tissue on histologic examinations found to be inflammatory. He was admitted to this clinic two years later with the history of persistent suprapubic fistula. There were two openings in the bladder of pin-head size, through which all the urine came. The child's mother said that when these closed, the patient ran a fever and had great difficulty in urinating, characterized by marked straining. Relief was obtained only by opening the suprapubic wound. On cystoscopic examination no evidence of tumor was found. The suprapubic fistulae were excised after which the bladder closed. For a short time after his return home the patient had little or no difficulty but it was not long before he had a return of the urinary obstruction with rise in temperature. In view of these symptoms it was thought probable that there was a contracture of the vesical neck which gave rise to the obstruction. Accordingly, on February 3, 1918, the bladder was opened and found to be of the size of a walnut. The vesical orifice was dilated, as was the entire posterior urethra, it being possible to introduce the index finger as far as the external sphincter. A catheter followed by a large sound was passed through the posterior urethra into the bulb. While no actual obstruction was demonstrated, it seems probable that the dilated posterior urethra was caused by a congenital obstruction in the membranous urethra and the case is therefore included in this report.

Case IX. This patient, aged twelve years, was admitted to the Johns Hopkins Hospital, May 18, 1915, with the history of difficult and frequent urination since birth. This was thought at first to be

due to a peno-scrotal hypospadias with contracture of the meatus. His general condition was negative except for a marked kypho-scoliosis. On abdominal examination the bladder could not be felt, but passing up from the bladder region to the costal margins a large, doughy, sausage-like mass could be felt on either side of the mid-line. Beneath the costal margin on either side large, soft structures, apparently kidneys, were palpable, the right being considerably larger than the left. The external genitalia were normal, except for a peno-scrotal hypospadias associated with considerable downward bending of the penis.

A small catheter was readily introduced withdrawing 700 cc. of cloudy, infected urine. Afterward the bladder was filled with fluid and a small cystoscope passed. Both ureteral orifices were markedly dilated and the bladder was quite trabeculated. No obstruction was seen at the prostatic orifice. A retention catheter was introduced. It was noted subsequently that 550 cc. of sterile water could be introduced without causing discomfort but when this amount was exceeded the patient cried out with sharp pain in his upper abdomen. A relatively small amount of this fluid was returned through the catheter and pressure over the suprapubic region did not increase the flow through the catheter. When pressure was made, however, over the kidneys and ureters the entire amount of water introduced was promptly returned.

Phenolsulphonphthalein two days after admission appeared in the urine in nineteen minutes, the output for the first hour being 15 per cent, 10 per cent for the second hour. A thorium X-ray was now made. A catheter was passed and the urinary tract emptied as completely as possible by pressure. Then 600 cc. of 10 per cent thorium citrate solution were introduced by gravity and the X-ray taken. A remarkable condition was found. The internal sphincter was quite widely dilated, measuring 1.25 cm. in diameter. The dilatation continued into the prostatic urethra for 1.5 cm., where it ended abruptly. The bladder showed a slight grade of hypertrophy and some irregularity in its contour suggesting trabeculation. Both ureters were widely dilated, the right measuring 3.5 cm. in diameter, the left measuring 2 cm. The left ureter was at least twice as long and more tortuous than the right. The right kidney showed a large, saccular hydronephrosis, measuring 12 by 8 cm. The left kidney was less dilated and measured 6 by 7.5 cm.

At operation the bladder was opened and found to be slightly dilated and considerably hypertrophied. The prostatic orifice was quite



FIG. 9. ROENTGENOGRAM MADE IN CASE 9 AFTER 600 cc. of 10 PER CENT THORIUM NITRATE HAD BEEN INTRODUCED INTO THE BLADDER BY GRAVITY

Note the dilated posterior urethra and vesical orifice, the irregular bladder outline and the distended ureters and kidneys.

dilated and the index finger could readily be passed into the prostatic urethra for a distance of 1 cm. At this point, however, a band of more or less crescentic shape extending across the roof of the urethra was found. A sound passed through the penile urethra could be made to enter the bladder with ease unless the beak was made to hug the superior wall. By means of a small rongeur the band was grasped and divided in three places. This diaphragm was quite fibrous. Subsequent histological examination showed it to consist of connective tissue and smooth muscle. After the removal of the obstruction, instruments could be passed without any difficulty.

The patient made an uneventful recovery from the operation and was discharged from the hospital in four weeks. He was voiding without the least difficulty and in a large forceful stream. Catheterization, however, recovered 150 cc. of residual urine which is explained very probably by the double hydronephrosis and hydroureter. The final phenolsulphonphthalein showed an output of 19 per cent for the first hour and 15 per cent for the second.

Case X. This patient, aged seventeen, was admitted to the hospital, November 11, 1912. He gave a history of having had difficulty since birth in passing urine, urinations having been accomplished only after several trials and marked straining. He had had to void every two hours during the day and once at night for as long as he could remember. There was no history of pain or incontinence. For nine years prior to his admission the urine was very cloudy. One month before coming to the hospital his eyesight became affected so that in reading, the printed page was blurred and objects at a distance were indistinct. There was no dizziness, no headache, no edema, no dyspnea.

On examination at the time of admission the patient was fairly well nourished, although his appearance was unhealthy and his complexion pasty and sallow. The general physical examination was negative, the positive findings being concerned only with the urinary tract.

On cystoscopy no obstruction to the passage of the cystoscope was encountered. There were 475 cc. of residual urine and the bladder capacity was 750 cc. No obstruction was found at the prostatic orifice; in fact, it was somewhat dilated. The bladder was considerably trabeculated and the right ureteral orifice widely dilated.

On examination of the urethra with the cysto-urethroscope a rather prominent ridge was seen coursing along the floor of the urethra in its mid-line between the external sphincter and the verumontanum. The ridge ended in the verumontanum which was of about normal

size. The upper aspect of the verumontanum was bifurcated and from it were continued two thin folds of tissue which were apparently attached to the floor and lateral walls of the urethra in the region of the internal sphincter. Neither ejaculatory duct could be seen but just beneath the internal sphincter there was an opening which measured, possibly, 3 mm. in diameter, which was probably a dilated utricle. Considerable pus was seen issuing from this. At a subsequent examination an attempt was made to pass a straight urethroscope but considerable difficulty was encountered in the region of the internal sphincter; a slight amount of force was used and the instrument passed into the bladder. Following this instrumentation the patient voided very much more freely; in fact, his urinary stream was about normal size. He held his urine for several hours and his former urinary symptoms largely disappeared. It seems very probable at the time of instrumentation the valve-like obstruction noted at a previous examination had been ruptured. The patient lived for a year with no return of his former urinary symptoms. He died of pneumonia.

Autopsy. The bladder was quite dilated and rather thin walled. The right ureteral orifice was quite markedly dilated, measuring at least 1.5 cm. in diameter. The right ureter was very tortuous and measured 4 cm. in diameter at its widest portion. The right kidney was a mere shell, containing apparently no renal tissue. The left ureteral orifice was well dilated, being only about a fourth as large as the right. This ureter was also quite tortuous and dilated, measuring, however, 2.5 cm. at its widest portion. The left kidney showed a considerable grade of hydronephrosis, the destruction, however, being much less marked than on the other side. The interesting feature of the post mortem study concerned the posterior urethra (see plate 5). Just beneath the internal sphincter was an opening more or less slit-like in character, passing from the lower region of the sphincter to the level of the verumontanum. On examination of the upper portion of the slit it was found possible to pass a large probe behind the bladder for a distance of 1 cm. The condition of the verumontanum was peculiar in that it was bifurcated, the concavity extending towards the bladder. From each leg of the "V" there continued upward toward the bladder a fibrous ridge which extended at least 3 mm. above the floor of the urethra. These ridges bounded the slit-like cavity noted above; they ended in the region of the internal sphincter which appeared to be quite widely dilated. On examination of the remainder of the posterior urethra only slight if any dilatation was seen. From the lower

aspect of the verumontanum and coursing along the mid-line of the urethral floor was a fairly prominent longitudinal ridge of tissue which rose from the surface of the urethra for about 1 mm. This finally bifurcated in the region of the prostatic apex and gradually disappeared. The remainder of the urethra appeared perfectly normal.

Case XI. This patient, aged twenty-six, was admitted to the hospital on March 7, 1916, with history of marked dysuria and urinary frequency for nine years, prior to which time he had no symptoms referable to the bladder. Upon examination the prostate was soft and atrophic but the seminal vesicles were enlarged and very hard. Both epididymes were enlarged, nodular and indurated. The bladder urine was infected and the renal function greatly reduced, there being but a trace of phenolsulphonphthalein appearing in the urine in two hours. Upon cystoscopy no difficulty was encountered in introducing the instrument. There were 175 cc. of residual urine. The bladder was moderately trabeculated and both ureteral orifices were normal in appearance. The internal sphincter showed considerable dilatation and the entire posterior urethra was quite dilated. The median portion of the prostate was flattened out and just in front of it were three very prominent ridges, more or less fan-like in character, which passed down the floor of the urethra ending in the verumontanum on either side of which was a rather deep pouch formation. Examination of the urethra below the verumontanum showed a large, prominent ridge passing down the mid-line for a distance of 1.5 cm. At its lowermost portion the right side of this ridge was found to be continuous with a prominent, fibrous-like septum which was attached to the urethra throughout half of its circumference. The left side of the urethra presented no such anomaly.

Operation. By means of the "punch" the septum was removed, this procedure being followed by very little bleeding. The operation, however, resulted in incontinence of urine when the patient was up and about, although when sitting or lying down, the patient was able to hold his urine from three to four hours. The urine was voided freely and in good stream. He left the hospital with 35 cc. of residual urine and a bladder capacity of 75 cc.

Case XII. Patient, aged forty-two, was admitted to the hospital, June 2, 1917, with history of urinary trouble dating from early childhood. He had always had marked hesitancy in starting the urinary stream, which was small and weak. Until the age of twenty he was constantly troubled with nocturnal enuresis and daily frequency of

urination. At the age of twenty-eight he contracted gonorrhea during the course of which he developed a urethral stricture, which was divided by internal urethrotomy, after which sounds to 40 F. could be passed. For ten years following this procedure his symptoms improved, although he still had considerable frequency and difficulty in voiding. At this time his urine became very cloudy, he had frequent attacks of chills and fever and suffered from pain in the region of the left kidney. From this time on his urinary difficulty increased; he voided at half-hourly intervals during the day and from ten to twelve times at night and as his symptoms increased he developed nocturnal incontinence. Six months before admission his bladder capacity was 1700 cc. Large sounds could be passed into the bladder but smaller instruments met an impassable obstruction in the prostatic urethra. Following the passage of sounds there was little or no improvement in his symptoms.

Upon examination at the time of admission the patient was fairly well nourished but pale and of a pasty, sallow color. Except for his uro-genital system no organic disease was made out. He was able to void a small amount of very cloudy urine in the sitting position but only after great straining. Upon rectal examination a marked prostatitis and seminal vasculitis were found and examination of the secretion expressed showed nothing but pus. Upon cystoscopy some difficulty was encountered in introducing the instrument owing to an obstruction at the mid-prostatic portion of the urethra. Upon withdrawing the instrument slightly and then greatly depressing the handle, it passed quite readily into the bladder, recovering 1100 cc. of cloudy urine. Study of the vesical orifice revealed nothing to account for the obstruction, in fact, the orifice and the prostatic urethra as far as the verumontanum showed considerable dilatation. The vesical mucosa was diffusely inflamed, there were no diverticula and the ureteral orifices were only slightly enlarged.

Further investigation of the posterior urethra with the cystourethroscope gave most interesting findings. Passing down the mid portion of the floor of the urethra between the internal sphincter and the verumontanum was a cylindrical body, apparently 3 or 4 mm. in diameter, on either side of which at about its mid portion was a shallow diverticulum. At the lower extremity of this cylindrical structure was an enlarged and globular verumontanum which at first suggested an explanation for the obstruction. Upon withdrawing the instrument farther, however, two valve-like folds were seen on either side of the

TABLE 4
Cases from the Urologic and Pediatric

CASE NUM- BER	DATE	AGE	SYMPTOMS	CLINICAL EXAMINATION	DIAGNOSIS
1	3-1-16	11 days	Vomiting; abdominal distension; urinary retention	Distended bladder; obstruction to catheter	Abdominal tumor
2	10-15-17	3 mos.	Loss of weight and vomiting	Pyuria	
3	7-14-14	6 mos.	None until 2 days before admission, then abdominal distension	Catheter met with obstruction at external sphincter	
4	7-30-16	15 mos.	Loss of weight; vomiting	Distended bladder; pyuria. Residual urine; reduced renal function	
5	8-25-13	20 mos.	Urinary difficulty and pain	Distended bladder; palpable mass in each kidney region; reduced renal function; X-ray to demonstrate point of obstruction	Congenital obstruction posterior urethra
6	8-19-13	21 mos.	Painful urination for 10 months. Periodical attacks of retention	Distended bladder; obstruction to catheter in posterior urethra; residual urine	
7	1-25-13	2 yrs.	Attacks of complete retention	Residual urine	
8	12- 8-17	4 yrs.	Dysuria. Persistent suprapubic fistula	Pyuria; persistent suprapubic fistula (post-operative)	Contracture of vesical neck
9	5-18-12	12 yrs.	Difficult and frequent urination since birth	Large residual urine; pyuria. obstruction to catheter, posterior urethra; cystogram; reduced renal function	Congenital obstruction

TREATMENT	OPERATIVE FINDINGS	AUTOPSY FINDINGS	RESULT	REMARKS
Exploratory laparotomy	Mesenteric and urachus cysts	Division crista urethralis below verumontanum into 2 valves Specimen destroyed	Dead Dead	
Suprapubic cystostomy with rupture of valve in posterior urethra with finger	Valve in mid portion prostatic urethra		Well	
		Two valves below level of verumontanum	Dead	
Suprapubic cystostomy with destruction of valve; clamp and cautery	Just below vesical orifice vertical valve on left side		Well	Died 1 year later of diphtheria
Suprapubic cystostomy with external urethrotomy, with rupture of valves; sounds	Three membranous folds below verumontanum		Well	
		One valve below verumontanum springing from lower end crista urethralis, left side	Dead	
Suprapubic cystostomy with passage of large sounds			Well	
Suprapubic cystostomy with destruction of valve; Rongeur	At about level verumontanum crescentic band across roof of urethra		Well	

TABLE 4
Cases from the Urologic and Pediatric

CASE NUM- BER	DATE	AGE	SYMPTOMS	CLINICAL EXAMINATION	DIAGNOSIS
10	11-11-12	17 yrs.	Urinary difficulty since birth	Residual urine; pyuria; urethroscope shows 2 thin valves springing from crista urethralis	Urethroscopy; congenital valves in posterior urethra
11	3-17-16	26 yrs.	Dysuria and urinary frequency for 9 years	Residual urine; pyuria; urethroscope shows 1 valve below verumontanum springing from crista urethralis	Urethroscopy; congenital valve in posterior urethra
12	6- 2-17	42 yrs.	Urinary difficulty since early childhood. Frequency; nocturnal enuresis	Residual urine; pyuria; urethroscope shows 2 valves springing from verumontanum running toward external sphincter; reduced renal function	Urethroscopy; congenital valves posterior urethra

Résumé: Of the 12 cases comprising this series, 8 were operated, 6 being cured and 2 admission to the hospital.

Concluded
Clinics—Johns Hopkins Hospital

TREATMENT	OPERATIVE FINDINGS	AUTOPSY FINDINGS	RESULT	REMARKS
Rupture of valves per urethram; urethroscope		Remains of valves (Type 2) previously destroyed. Enlarged utricle; bilateral hydroureter and hydro-nephrosis.	Well	Patient died of pneumonia 1 year later; see autopsy findings
Excision of valve with "punch"	Single valve on right side of urethra below verumontanum.		Well	Excision followed by partial incontinence
Excision of 1 valve with "punch"	Bilateral valves of urethra below verumontanum.		Well	Marked improvement

markedly improved. Four cases were not operated upon, all but one dying shortly after

mid-line, stretching between the verumontanum and the bulbo-membranous junction. These folds were apparently quite thin and at their point of origin from the anterior aspect of the verumontanum closely approached each other, taking, however, a more or less divergent course as they passed on to their insertion in the region of the bulb. It was possible to demonstrate further the more or less curtain-like character of these structures by watching their excursion when the irrigation fluid was passing through the urethra. While they caused no obstruction to the introduction of fluid their divergent course between the verumontanum and the bulb would offer considerable difficulty to the passage of urine.

The renal function at the time of admission was greatly reduced, there being but a trace of the phenolsulphonphthalein excreted in two hours. The blood urea ranged between 0.75 and 0.80 gram to the liter.

Upon ureteral catheterization no ureteral obstruction was encountered. The urine from the right kidney was fairly clear but microscopically showed pus and a staphylococcus infection. Semi-fluid pus was recovered through the left catheter, the condition on this side being one of pyonephrosis. Pyelography on the right revealed a hydronephrosis and some ureteral dilatation.

Operation. This was carried out per urethram by means of the punch instrument. The bladder was first irrigated, filled with water, after which the punch was introduced, withdrawn, turned slightly to the right catching the valve in the fenestra; this was then removed by the circular knife. The same procedure was carried out on the left side. There was practically no bleeding and a small retention catheter was introduced.

Post-operative course. At the time of discharge on August 18, 1917, there was still between 200 and 300 cc. of residual urine. The patient, however, voided with ease and passed his urine at five hourly intervals. He was advised to catheterize himself twice daily. When last heard from, in May, 1919, the patient was practically free of urinary symptoms, holding his urine all night and voiding as much as a pint at a time in a large, forceful stream.

CASES FROM THE LITERATURE

The literature of the condition has been reviewed because it seemed desirable to have at hand every possible case from which to draw our inferences. The 24 cases of which we give below

the salient factors do not, of course, exhaust the mention of the condition in the literature, but they do cover fairly completely the definite reports of cases. They are presented here in an order which depends upon the age of the patient at the time of death or operation.

1. *Case of Fuchs (1)*. Report of autopsy on fetus between fifth and sixth month. Running anteriorly from the verumontanum was a ridge which split after several millimeters into two folds which diverged to the two sides of the urethra where they became attached. These folds formed a pocket with its concavity toward the bladder. The prostatic urethra was much dilated, particularly on the posterior wall, the verumontanum lying in the depression. Following the sinus prostaticus and the ejaculatory ducts with a probe, one was led into a cavity about the size of a pigeon's egg, lying behind the bladder. It was evidently formed by a fusion of the seminal vesicles with the sinus prostaticus. The vasa deferentia lost themselves in the walls of this cavity. The bladder was hypertrophied and dilated, the ureters were dilated, tortuous, the left being longer than the right. There was an hydronephrosis present.

2. *Case of Fuchs (1)*. Report on autopsy on full term still-born baby. The verumontanum extended downward along the floor of the urethra in a ridge which divided into two processes. These joined the lateral walls of the urethra, forming valves, which had their concave surfaces toward the bladder. There was a narrow slit between the two cusps. From the upper end of the verumontanum a number of fine folds radiated toward the bladder. Dilatation and hypertrophy of bladder, hydroureters, hydronephrosis.

3. *Case of Commandateur (2)*. Following a normal delivery, the baby breathed ineffectually a few times and died. The body was that of a boy weighing 3100 grams. There were no external malformations. The bladder reached to the liver margin. Urine:—specific gravity 1:031. Albumin—heavy precipitate. Ureters much dilated. Kidneys cystic, dilated. Bladder dilated, hypertrophied, trabeculated. Urethra: a sound passed from below met with an obstruction. At the lower end of the verumontanum there was found a delicate valve-like structure which was attached to the floor of the urethra. When not under tension it fell to the lower wall of the urethra almost unnoticed; when ballooned out, however, it practically occluded the urethral canal.

4. *Case of Schlagenhauser (3)*. A boy died twenty minutes after birth with increasing cyanosis.

Autopsy. Hydronephrosis, hydroureters, hypertrophy and dilatation of the bladder. The prostatic urethra was in free communication with the bladder and the internal sphincter dilated, its wall was thickened and bulged outward. "At the point where the verumontanum usually tapers off into the two low ridges which run forward, outlining a shallow depression between them, one sees the unusually fine opening of the urethra. This opening occurs at the summit of a cone formed by folds which run down to join the mucosa of the urethra in deep pockets.

"At first, attempted catheterization from the bladder forward, even with a fine probe, was unsuccessful, . . . from below, however, a relatively large sound passed readily into the prostatic urethra."

5. *Case of Bednar* (4). A premature boy was seen soon after birth. Infant weak, muscles lax, voice loud, cry that of pain. The umbilicus protruded and was pus covered. At first the child nursed haltingly. On the tenth day he was too weak to nurse and the abdomen as very distended. He died on the twelfth day with evidences of beginning pneumonia. He had not voided for five days.

Autopsy. Pus was found in the umbilical artery and hepatization of the lower lobes of the lungs with pleuritic effusion. The verumontanum divided at its forward end into two folds of mucous membrane which were half-moon shaped and concave towards the bladder. These folds freely admitted the passage of probe from below but on pressure from above ballooned out so as to close the lumen. The external genitalia were normal. The bladder wall was three times normal in thickness. The ureters were widened, and there was a double hydronephrosis with atrophy of the kidney substance.

6. *Case of Jordan* (5). At four weeks of age a male infant was noticed to dribble urine continuously; at seven weeks he died. Autopsy showed a fibrous stricture of the posterior urethra, a small bladder, hydroureters, the right being larger than the left, cystic kidneys and chronic diffuse nephritis.

7. *Case of Fletcher* (6). Male infant of three months admitted to the hospital for abdominal distention. At six weeks he had had convulsions and during the four weeks previous to admission had developed a gradually increasing abdominal distention. Examination showed a poorly nourished, anemic baby, with abdomen distended and tympanitic, its skin surface smooth and shiny. To the left a large tumor was felt, practically filling the left upper quadrant. In the upper right quadrant a small mass could be felt below the liver mar-

gin. Above the symphysis a third large round mass reached nearly to the umbilicus. Frequent loose stools. Urination apparently normal. W. B. C. 25,000. Impression: Sarcoma of the bladder.

Operation. An abdominal incision was made but patient's condition was so bad that the abdomen was closed without anything being done. The patient died the following day.

Autopsy. The left kidney, with dilated pelvis formed a tumor twice the size of a new born baby's head. The renal parenchyma was apparently normal. The right kidney was similarly involved but to a lesser degree. The ureters were dilated and tortuous, and the bladder dilated and hypertrophied. "Stretching across the posterior portion of the urethra was a thin membranous septum, formed apparently by a projection of the mucous membrane of the posterior part of the circumference of the urethra." This formed an incomplete diaphragm with its free edge toward the bladder. There was a loose tag of tissue attached to the free edge of the valve which further occluded the opening.

8. *Case of Lowsley (7).* A boy, three and one-half months old, was brought to the Bellevue Hospital desperately ill. His temperature was 105°. He died a few hours later with edema of the lungs. The only history obtained was that the baby had been ill for a few days only, during which time the mother had noticed nothing unusual about his urination.

Autopsy. The verumontanum measured 3 mm. in height and was 3 mm. wide at its broadest point. Stretching from it were 6 small bands which extended backward to the internal sphincter. Extending downward from the verumontanum on the floor of the urethra was a thick band of tissue which continued downward to the membranous urethra "where it divided into two portions and then attached itself intimately to the entire urethral circumference, with the exception of a small slit-like opening on the floor of the urethra just to the left of the median line." This caused almost complete obstruction to the urinary outflow. The bladder was much hypertrophied. The prostatic urethra was dilated to such an extent that it was continuous with the bladder. The ureters were dilated and tortuous. The left kidney was larger than the right, both were dilated and cystic. The right cord was involved in a very large hydrocele; otherwise the external genitalia were normal.

9. *Case of Lindeman (8).* A boy of four months was admitted to the hospital. There was a marked edema, particularly of the eyelids and

lower extremities. There was no fever and no convulsions. The patient died soon after admission, without a diagnosis having been made. He did not void after entering the hospital.

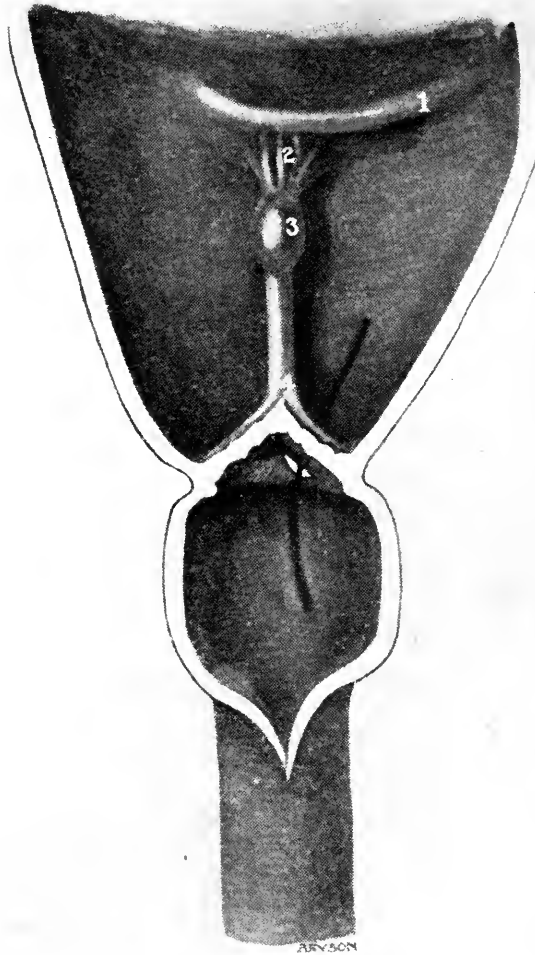


FIG. 10. DIAGRAM FROM LOWSLEY'S ARTICLE

(See Ann. Surg., lx, 1914.) 1, Dilated internal sphincter; 2, folds running from internal sphincter to verumontanum; 3, verumontanum; 4, bifurcation of crista urethralis. Probe passes through slit-like opening in obstruction. See case 8.

Autopsy. The left kidney was hydronephrotic and showed but little kidney tissue remaining; the right kidney showed a somewhat greater destruction. Both ureters were greatly dilated. "In the preparation which was made by cutting the urethra along its upper wall, the isthmus urethrae seems to be made up of two pockets similar to the fingers of a glove, divergent to the pars bulbosa; each of these pockets is 1 cm. in diameter; and between them the pars pendula insinuates itself. The pars pendula averages 6 mm. in diameter here as it does further down in its course. The bulging out of the isthmus mentioned above ends in blind pockets. The connection between them and the pars pendula is through a very narrow slit which measures barely 3 mm. and is found at the point of divergence of the folds."

10. *Case of Morton (9).* A boy of thirteen months had been ill for three months with wasting, vomiting and distended abdomen. Examination showed a hypogastric mass, evidently the bladder, which disappeared on catheterization. The urine obtained in this way showed blood and pus. The temperature ranged from 101° to 102° F. Death.

Autopsy. Hydronephrosis, hydroureters, hypertrophied bladder. "A small valve fold was found in the roof of the urethra just beyond the vesical orifice, directed downward and backward so that although the passage of the urine would be much interfered with, a catheter would not be obstructed."

11. *Case of Thompson (10).* A boy of fourteen months. For three months he had been constipated. Urination had evidently been painful, there was much straining and the act was accompanied by anal prolapse. Pus had recently been noted in the urine. Upon examination a mass was found in the lower abdomen which did not disappear on catheterization. An abdominal incision was made, the mass was found to be the bladder, which was opened and a drainage tube inserted. The patient died.

Autopsy. Hydronephrosis, hydroureters, hypertrophy and dilatation of the bladder. At the junction of the vesical orifice with the prostatic urethra was found a "diaphanous membranous septum lying flush with the wall of the open urethra." "A small opening must have existed in this, but that it was small was shown by the fact that the membrane appeared nearly complete."

12. *Case of Wilckens (11).* A boy of two and one-half years who had been previously well, developed diphtheria and after an illness of ten days was tracheotomised. The following day he had a number of convulsions and died.

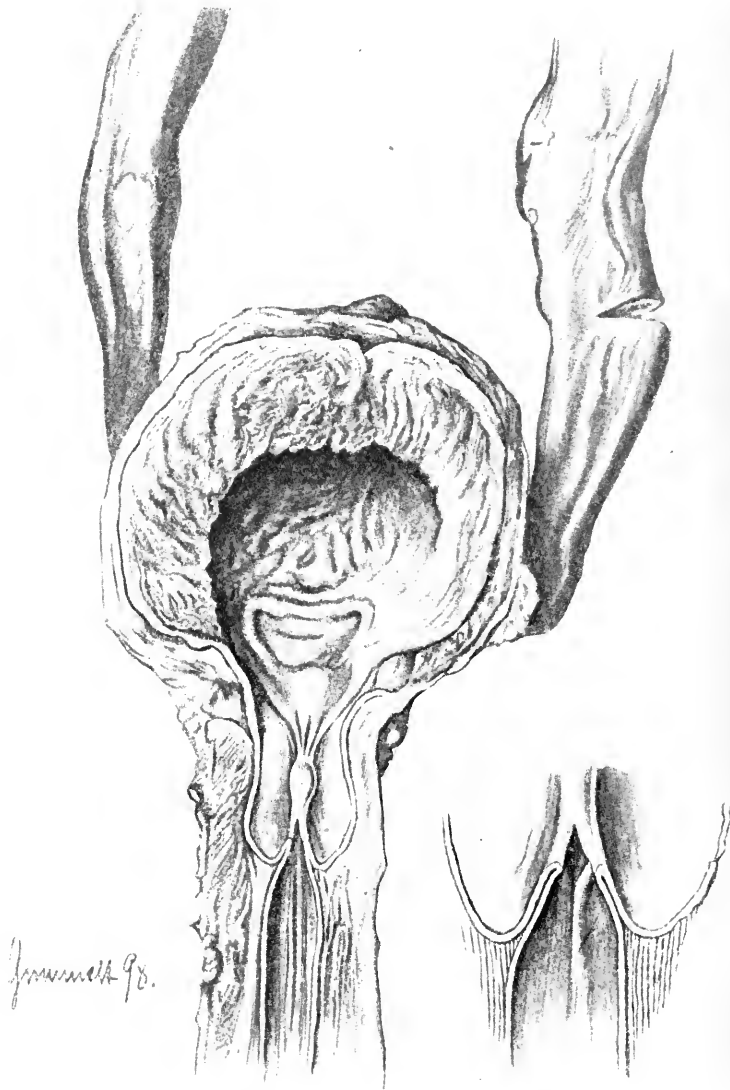


FIG. 11. ILLUSTRATION SHOWING VALVES OF TYPE I

Showing dilatation of posterior urethra, hypertrophied bladder and hydro-ureters. Insert gives detail of valve formation. Lindeman, F. P., Inaug. Dis., Jena, 1904. See case 9.

Autopsy. Genito-urinary findings: The pendulous urethra was normal. "At the point of transition from the pars membranacea into the pars prostatic urethrae, but lying for the most part in the pars membranacea, there are two folds on the two sides of the urethra which course '*von hinten oben nach vorne unten.*'" (Because of an evident error in the German text, this clause is left untranslated.) These folds of mucous membrane are drawn out into the valves in the lumen of the urethra. In this way pockets are formed on the two sides, whose concavity is turned toward the bladder. On the anterior wall of the urethra these folds almost but not quite touch. On the posterior wall they fuse . . . and join the ridge which is formed by the prolongation of the colliculus seminalis downward along the midline."

13. *Case of Lindeman* (8). A four year old boy was brought to the hospital with the history of having been acutely ill for eight days. There were no further details. Examination showed nasal, tonsillar and pharyngeal diphtheria, with extension into the larynx, consequent dyspnea and retraction of the soft parts on inspiration. There were petechial hemorrhages. The patient was tracheotomised, dying twelve hours later.

Autopsy. There were the usual findings of a severe upper respiratory diphtheria. The bladder was hypertrophied and the pars prostatica and isthmus urethrae much dilated. The verumontanum was unusually prominent and stretching downward from it in a fanlike arrangement were five large folds and further to one side one small fold. The median fold was the largest, measuring 1 cm. These folds shut off communication between the isthmus and the anterior urethra except for a narrow slit 3 mm. in length, situated at the point of divergence of the folds. The external genitalia were normal. The kidneys were hydronephrotic, the left kidney atrophic. Both ureters were widely dilated.

14. *Case of Heinecke* (12). A boy of five years had difficulty in urination since birth. Urination took from twenty to twenty-five minutes. In the intervals between urination he dribbled constantly, always being wet. He had frequently been catheterized for retention and it was noted that the catheter met with an obstruction just before entering the bladder. For three months previous to admission he had an evening elevation of temperature frequently as high as 40°C.

Examination showed a normally developed, pale boy. The bladder was large and readily palpable and there was constant dribbling of urine. Two or three times daily the patient urinated a very thin



FIG. 12. ILLUSTRATION SHOWING FOLDS ORIGINATING AT VERUMONTANUM,
OBSTRUCTING POSTERIOR URETHRA

From article by Heinecke, E. *Zeitschr. f. Urol.*, vii. See case 14.

stream, the act taking about one-half hour. Upon catheterization a large amount of urine was obtained, showing pus and albumin but no casts. Ten days after admission the patient became worse, catheterization was difficult and a suprapubic cystostomy was carried out. The patient died a few hours later.

Autopsy. The primary lesion was found in the posterior urethra. "Upon opening the urethra, the lumen appeared nowhere to be widened or narrowed. From the verumontanum two half-moon shaped folds stretched downward in gentle curves, to be attached to the two sides of the urethra. In this way the pars prostatica is shut off from the pars membranacea as by two barriers." The bladder wall was thickened in both musculosa and mucosa. There were hemorrhages in the mucous membrane. The external genitalia were normal. The ureters were widened, the left being larger than the right. The kidneys were hydronephrotic, many abscesses being found in the kidney substance, particularly on the left side. Microscopic examination showed the valves to be composed of mucous membrane over loose connective tissue in which were a few smooth muscle fibers.

15. *Case of Knox and Sprunt (13).* A boy, aged five years, had always had to wear napkins which he wet about every half hour. The urine was often thick and milk-like. Otherwise his history was uneventful till three years of age when he had measles, following which he had a chronic otitis media. When seen he complained of loss of weight, loss of strength and diarrhea. Examination showed a pale, emaciated boy, with evidence of rickets. The abdomen was distended. In the left lumbar region a soft movable lobulated mass could be felt, extending upward to the costal margin. A similar mass could be made out on the right side, below the edge of the liver. A third rounded mass extended in the mid-line from the pubis to the umbilicus. The external genitalia were normal except for the fact that the external meatus was too small to admit the smallest catheter available. The urine was acid, the specific gravity 1.002 to 1.004, containing a faint trace of albumin, no sugar but many pus cells and red blood cells. He was lost sight of for six months and then admitted to the Medical Service of the Johns Hopkins Hospital. Two months before, he had developed a cough and abdominal pain, since which time he had become progressively worse. He was pale and extremely ill. The breath sounds were harsh and there were a few râles. The abdomen was distended and a number of soft coils, thought to be intestines, were made out. Above the symphysis and reaching nearly to the

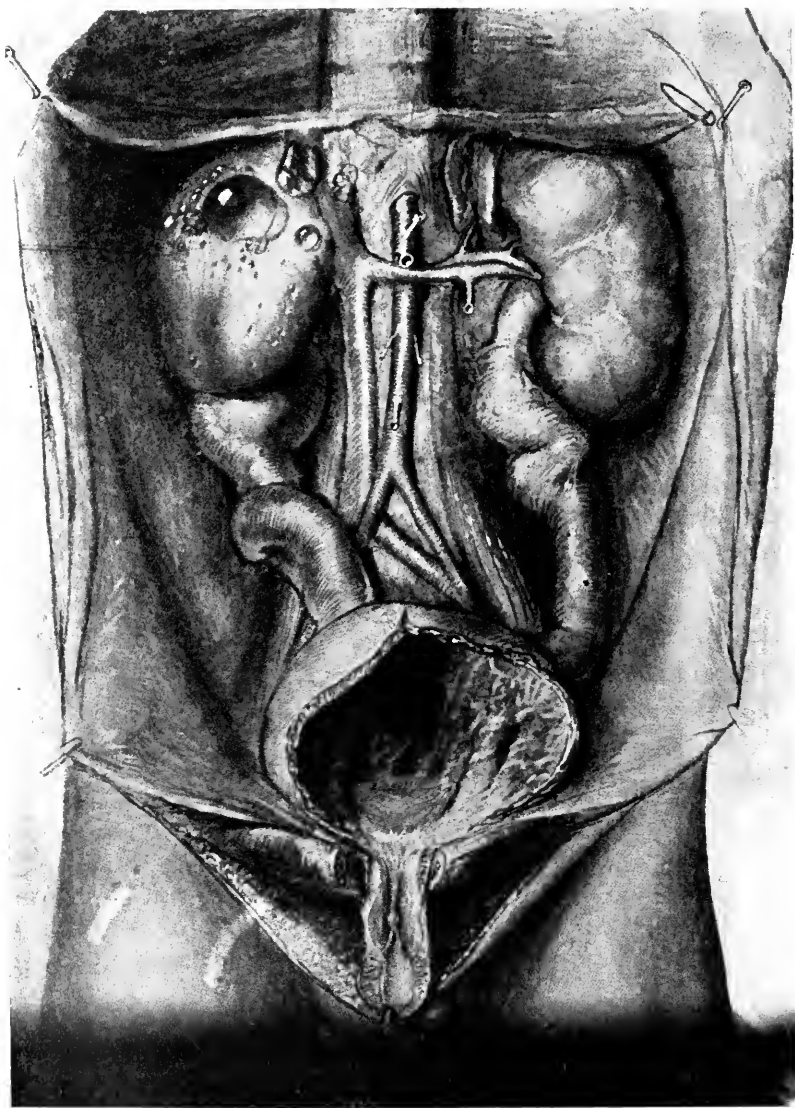


FIG. 13. SHOWING SPECIMEN OF CASE REPORTED BY KNOX AND SPRUNT
See Amer. Jour. Dis. Child., lv, 1912. See case 15.

umbilicus was an oval mass thought to be the bladder. The urine contained pus and a trace of albumin. X-ray after a bismuth meal showed the stomach to be slightly dilated but the motility was normal. There was unusual stasis between the sigmoid and the rectum. The child's condition became progressively worse and after repeated convulsions he died.

Autopsy. "Through the wide internal meatus the bladder becomes continuous with the greatly dilated and thick walled prostatic urethra which forms an oval sac with the distal, blind extremity 2.5 cm. from the internal meatus. The floor of this pouch shows several prominent folds near the mid-line, which end below in an unusually prominent verumontanum which reaches three-fifths of the distance from the internal meatus to the blind end of the sac. The opening of the vagina masculina is conspicuous, shaped like a crescent, with the concavity directed upward. Numerous orifices of the prostatic ducts are observed on each side of the verumontanum, but those of the ejaculatory ducts are not seen. Immediately below the verumontanum the ridge of which it forms a part, divides into two prominent diverging folds which soon fuse with the anterior wall of the urethra instead of fading out gradually on the posterior wall of the membranous urethra as usual. Just below the verumontanum between the diverging folds, there is a small equilateral triangular opening whose sides measure about 3 mm. A probe passed through from the anterior urethra presents in this opening and abuts against the hypertrophied verumontanum. This is the only communication between the anterior and posterior portions of the urethra." The bladder was dilated, hypertrophied and trabeculated. There were scattered ecchymoses in the mucosa. The ureters were tortuous, enlarged, thickened. The kidneys were hydronephrotic, the left being larger than the right.

16. *Case of Lindeman* (8). A strongly built, five and one-half year old boy, was admitted to the hospital. The physical examination was negative except that resistance could be made out in the bladder region. He voided only in a thin stream. He had no pain, no convulsions, but went from bad to worse and died without a diagnosis having been made.

Autopsy. Double hydronephrosis with atrophy of the kidney substance. The ureters were dilated widely, thick walled and tortuous. The bladder was hypertrophied. The pars prostatica and isthmus were wide. From the posterior limit of the verumontanum ran three folds diverging toward the bladder. From the anterior end ran two

other folds which formed valves shutting off the urethra except for a narrow slit.

17. *Case of Lederer* (14). A boy previously considered well, had scarlet fever at six or seven years. There was no record of any renal complication. However, following the attack he suffered from difficulty of urination, long straining being necessary to start the stream, upon which he would pass large amounts of reddish urine, with white or yellow shreds. He suffered from incontinence both day and night. He was always sickly and pale. There was no swelling of the feet. After going on in this manner for several years he became suddenly ill with dyspnea and swelling of the face and was admitted to the hospital. Examination: Eleven year old boy, well developed, fairly well nourished, pale, edematous. Cheeks, lips and nose were cyanotic. The throat was pale and slightly edematous. Respiration was deep and there were many râles. The heart action was rapid and weak. He was vomiting. The urine showed albumin; red blood cells but no casts. The diagnosis made was uremia following old scarlet nephritis. He died forty-eight hours after admission.

Autopsy. Both kidneys were large and hydronephrotic, particularly the left, which was filled with blood stained fluid and clots. The right was filled with pale, slightly turbid fluid. Both kidneys were divided by septa into many small compartments. Here and there on the walls of the compartments were bits of the kidney tissue. The ureters were both dilated to many times their normal size. The bladder was pear shaped and trabeculated. Upon trying to pass a sound from the bladder, resistance was encountered in the first part of the membranous urethra. This resistance was also met with in passing a sound upward from the meatus. One centimeter below the verumontanum there was a semicircular diaphragm with its concavity upward. This entirely closed off the urethra except for an opening about the size of a hemp seed in the posterior part. This opening lay at the end of a fibrous band stretching down from the verumontanum. There was great dilatation of the prostatic urethra which resembled the bladder closely in its mucosa. The internal sphincter could be located by the muscle fibers which shone through the mucosa. The external genitalia were normal except for phimosis.

18. *Case of Posner* (15). Boy, aged eleven years had been well until he had an attack of scarlet fever. Soon after this he developed pyelitis, with pain in the right kidney region, pus in the urine and hematuria. Examination showed a large bladder. This was catheter-

ized and 1100 cc. of purulent urine obtained. The author felt that that might be but a chance finding, so, on frequent occasions he repeated the catheterization. On each repetition he found residual urine which decreased from the original large amount until it was reduced to 10 cc. The catheter always overcame a resistance encountered in the bulbar region, and he felt that there was a stricture there, which he believed to be congenital in origin.

19. *Case of Budd* (16). A sailor, aged sixteen years, was admitted unconscious, dying in two days.

Autopsy. The renal pelves were dilated, the kidneys being but thin walled sacs. The ureters were as large as intestines. The bladder was hypertrophied and dilated. In the upper wall of the membranous urethra was a fold of membrane similar to the valve in a vein.

20. *Case of Bazy* (17). A young soldier came in complaining of incontinence over a period of many months, preceded by difficult urination dating back to early infancy. He had crises of retention. Instrumentation always met with an obstruction in the posterior urethra. Perineal operation: The membrane occupied the entire periphery of the canal, decreasing the caliber greatly. It was made of two folds between which there was a narrow slit. It lay in the bulbous urethra. The folds were resected. Cure.

In the same article the author reviews six cases which he had formerly reported (18) in which, while there was no operation or autopsy, he felt sure there were valve-like processes. Four had come to him for incontinence, one for bacilluria and one for dysuria. In each case he felt on passing a sound a peculiar resistance about 1 cm. beyond the external sphincter. More recently Artus (19) has reported from Bazy's Clinic two further cases, in boys five and seven years old, respectively, which were admitted for incontinence. These cases were cured by instrumentation and the author presented them as examples of congenital stricture. It should be noted that in none of these case reports is any mention made of the presence of residual urine, dilated bladder or other evidence of urinary back pressure. The diagnosis was made apparently on the mere passage of a sound which encountered resistance in the region of the external sphincter. While these cases may be examples of congenital obstruction, the evidence at hand is not conclusive, and the exact site of the obstruction is not certain.

21. *Case of Picard* (20). A brewer, forty years of age, of an athletic build, came to the hospital, complaining of cough and difficult urination. He was fully conscious. While undressing he fell unconscious,

frothing at the mouth, his extremities moving convulsively. He was bled and after half an hour recovered somewhat. On examination there was slight edema of the lower extremities. The bladder was palpable. There was no evidence of paralysis. A diagnosis of uremia

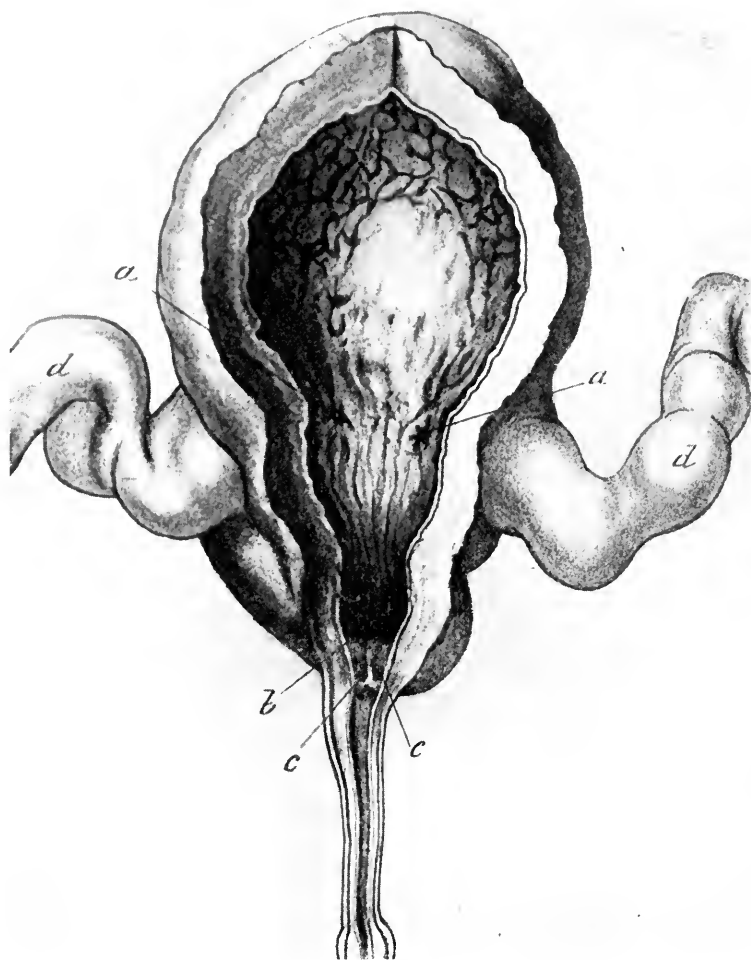


FIG. 14. ILLUSTRATION SHOWING RESULT OF FAIRLY COMPLETE OBSTRUCTION ON POSTERIOR URETHRA, BLADDER AND URETERS

The valves are of type 1. From article by Tolmatschew in *Archiv. f. Path. Anat.*, 1870, 11. See case 24.

was made and the patient was catheterized. The catheter met with resistance and a smaller one was introduced. The patient became suddenly much worse and died in four minutes. He was catheterized post mortem, the urine being milky, acid and containing albumin.

Autopsy. Revealed congestion of the brain and some peritoneal fluid. Anterior to the verumontanum and 3 mm. to the side of the mid-line was a fold of resistant connective tissue. It was attached to the floor of the urethra in a diagonal direction, with its free edge upward. A small catheter introduced from below passed this valve, but on forcing fluid from above it was ballooned out. The bladder wall was thickened, the ureters dilated, and the kidneys damaged from pressure of the urine in the pelves. It later developed that four years previously the patient had had an attack of urinary retention and incontinence which had been relieved by catheterization.

22. *Case of Iverson (21).* A man, eighty-five years old, had difficulty in urinating and frequently passed blood. The bladder could be felt reaching the umbilicus. Repeated catheterization failed to recover any urine and it was felt that there might be a false passage. A large prostate was palpable rectally. The patient was very uremic and soon died.

Autopsy. Showed marked dilatation of the prostatic urethra. The crista urethralis divided into two thin valves which formed a cup-like obstruction in the urethra.

The following cases fall out of series, as the age is not given:

23. *Case of Godart (22).* *Autopsy.* "In the urethral canal on one side of the verumontanum, one sees a membranous valve, very fine and delicate. The free edge is inclined toward the bladder."

24. *Case of Tolmatschew (23).* No history or physical examination. "The principal interest in the urinary apparatus lay in the presence of the valves in the urethra. These originated from a ridge, 8 mm. long, 1 mm. broad and 0.5 mm. in height, which starting at the anterior end of the verumontanum ran downward along the floor of the urethra. This ridge separated into two thin membranes, which attached themselves one to the right, one to the left half of the urethra. Each of these membranes was attached by its anterior margin, in a semicircular fashion, to the wall, while the free margin was directed backward, thus forming a pocket, concave toward the bladder. In the mid-line, both anteriorly and posteriorly, these pockets were in apposition." The lower part of the urethra was normal. That part of the urethra lying above the valves was enlarged and the internal

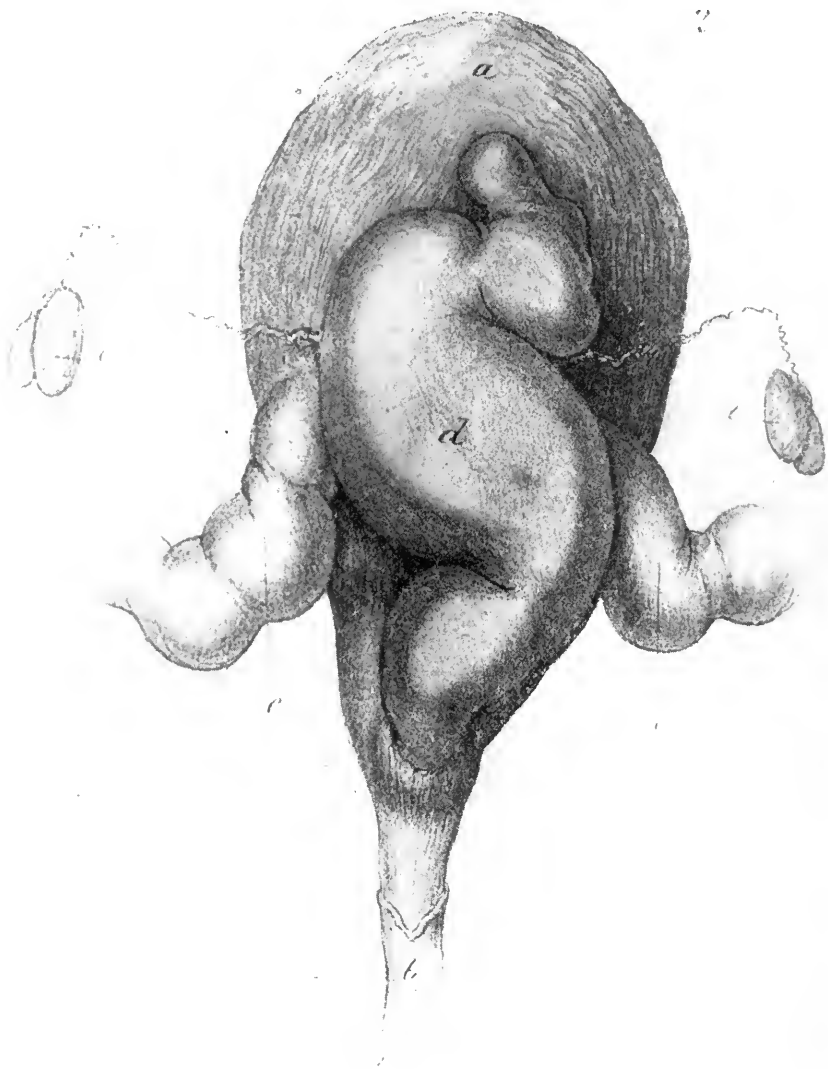


FIG. 15. POSTERIOR VIEW OF TOLMATSCHEW'S CASE

Showing enormous size of utriculus prostaticus. Archiv f. Path. Anat., 1870, 11. See case 24.

sphincter was obliterated. The verumontanum was pushed downward into a depression in the floor of the urethra and was brought up for examination only with difficulty. Its size and form were normal. In the center of it was found the opening of the utriculus prostaticus which on probing, was found to lead into a cavity lying behind the bladder. The bladder was enlarged, increased in length and pear shaped. The walls were hypertrophied. Behind the bladder and connected with it through the opening of the verumontanum lay a thin walled multilocular sac, which was filled with urine. It was lined with pavement epithelium which, in the lower part, resembled that of the vagina.

In addition to these cases it is interesting to note from an historical standpoint that Velpeau (24, 25), in 1832 described folds in the posterior urethra which resembled valves, and mentions the possibility of their causing obstruction to the passage of a catheter. Jarjavay (26) in his interesting monograph on the urethra published in 1856 mentions folds at the bifurcation of the crista urethrae, and states that he has also seen in the anterior portion of the pars prostatica, a circular membrane with its periphery attached to the urethral wall, having in its center an opening 3 mm. in diameter. This membrane he likened to the iris. Both he and Velpeau mention an article by Langenbeck (27) written in 1802 in which a mention is made of congenital valvular obstruction of the posterior urethra. So far as we can determine this is the first reference to the condition in the literature.

TABLE
Cases collected

NUM- BER	AUTHOR	DATE	AGE	SYMPTOMS	CLINICAL EXAMINATION
1	Fuchs	1900	5 mos. fetus		
2	Fuchs	1900	Full term fetus		
3	Commandateur	1898	Died at birth		
4	Schlagenhauser	1896	Died at birth		
5	Bednar	1847	12 days	Weak; abdominal dis- tension	Distended abdomen
6	Jordan	1913	4 wks.	Urinary incontinence	
7	Fletcher	1908	3 mos.	Convulsions; abdomi- nal distension; uri- nation normal	Distended bladder large tumor left u- per quadrant; small tumor right upper quadrant.
8	Lowsley	1914	3½ mos.	Only ill "few days," urination normal	Edema of lungs; tem- perature 105°
9	Lindeman	1904	4 mos.		Edema eyelids and lower extremities "Did not void after entering hospital"

from the literature

DIAGNOSIS	TREATMENT	OPERATIVE FINDINGS	AUTOPSY FINDINGS	RESULT	REMARKS
Sarcoma of the bladder	Operation (abdominal) attempted but stopped account of patient's condition		Division crista urethrae below verumontanum forming two valves	Dead	
			Division crista urethrae below verumontanum forming two valves	Dead	
			Delicate valves attached to floor of urethra at lower end of verumontanum	Dead	
			Funnel shaped valve attached to lower aspect of verumontanum	Dead	
			Verumontanum at lower end divided into two crescentic folds	Dead	
			"Fibrous stricture," posterior urethra	Dead	
			Membranous septum posterior urethra	Dead	
			Division crista urethrae below verumontanum forming two valves	Dead	
			Two folds below verumontanum	Dead	

TABLE 2
Cases collected

NUMBER	AUTHOR	DATE	AGE	SYMPTOMS	CLINICAL EXAMINATION
10	Morton	1903 1904	13 mos.	Wasting; vomiting; distended abdomen	Distended bladder; catheterization; py- uria
11	Thompson	1907	14 mos.	Urination painful and difficult	Distended bladder; catheterization; py- uria
12	Wilckens	1910	2½ yrs.	Diphtheria; previously well	
13	Lindeman	1904	4 yrs.	Acutely ill for 8 days	Diphtheria
14	Heinecke	1913	5 yrs.	Difficult urination since birth; incont- inence; frequency; frequent urinary re- tention	Distended bladder; py- uria; catheter met obstruction in deep urethra
15	Knox-Sprunt	1912	5 yrs.	Urinary frequency since birth; lost weight and strength	Distended bladder; palpable masses in region of kidney
16	Lindeman	1904	5½ yrs.	Difficult urination	Resistance in bladder
17	Lederer	1911	11 yrs.	Well for 6 years. Fol- lowing scarlet fever, dysuria, incont- inence, edema	Albuminuria
18	Posner	1907	11 yrs.	Following scarlet fe- ver, pain in right kidney, pyuria, he- maturia	Dilated bladder; cath- eter obstruction in bulbous urethra Residual urine 1100 cc.
19	Budd	1840	16 yrs.	Unconsciousness	

Continued
from the literature

DIAGNOSIS	TREATMENT	OPERATIVE FINDINGS	AUTOPSY FINDINGS	RESULT	REMARKS
Obstruction to urination in deep urethra	Suprapubic cystostomy	Distended bladder	Valve just below internal sphincter in roof of urethra	Dead	
			Membranous septum just below internal sphincter	Dead	
			Division crista urethrae below verumontanum forming 2 valves	Dead	
			Six folds below verumontanum	Dead	
			Verumontanum at lower end divided into 2 crescentic folds	Dead	
			Division crista urethrae below verumontanum forming two valves	Dead	
			Two folds from anterior aspect verumontanum forming valves	Dead	
			At end of crista urethrae below verumontanum semi-circular diaphragm	Dead	
Uremia					
Congenital stricture bulbous urethra	Frequent catheterization			Cured	Diagnosis; not confirmed. Obstruction bulbous urethra
			Membranous fold in upper wall membranous urethra	Dead	

TABLE 5-
Cases collected

NUM- BER	AUTHOR	DATE	AGE	SYMPTOMS	CLINICAL EXAMINATION
20	Picard	1855	40 yrs.	Difficult urination; uremia	Edema lower extremities; enlarged bladder; obstruction in posterior urethra
21	Iverson	1914	25 yrs.	Difficult urination; hematuria	Dilated bladder; catheter could not be introduced into bladder
22	Godart	1854	?	Not given	Not given
23	Tolmatschew	1870	?	Not given	Not given

Résumé: Of the 23 cases reported in the literature, 22 were dead, the anomaly being while another case was treated by catheterization without operation. In none of the cases

*Concluded
from the literature*

DIAGNOSIS	TREATMENT	OPERATIVE FINDINGS	AUTOPSY FINDINGS	RESULT	REMARKS
Obstruction in posterior urethra			One valve below verumontanum in floor of prostatic urethra	Dead	
False passage			Division of crista urethrae into 2 valves	Dead	
Not made	None		Membranous valve on one side verumontanum	Dead	
Not made	None		Division crista urethrae below verumontanum into 2 valves	Dead	

discovered post mortem. Two of the fatal cases were operated by suprapubic cystostomy, was any operation carried out for the cure of the valvular obstruction.

SUMMARY

1. *Frequency.* A review of the literature has revealed twenty-four authenticated cases of congenital obstruction of the posterior urethra; while in the last six years there have been admitted to The Johns Hopkins Hospital twelve cases showing this condition. It is therefore considerably more frequent than would be inferred from the attention given it in the past.

2. *Etiology and pathology.* Autopsy studies have shown that there are three distinct types of congenital obstruction, all more or less valvular in construction, so placed that the concave surface of the valve is directed upward, thus bringing about an obstruction to the outflow of urine. In the great majority of cases symptoms of the condition are manifest during infancy or early childhood.

3. *Symptoms* of the condition are those arising from obstruction to the outflow of urine together with the symptoms resulting from renal destruction, induced by back pressure and infection.

4. *Diagnosis.* The history of symptoms of urinary obstruction in male children should always suggest the possibility of this condition. The presence of a distended bladder and particularly of residual urine is further indicative of obstruction. This possibility is further strengthened by obstruction in the posterior urethra to the passage of a catheter. Much information regarding the character and exact location of the valves and the renal damage resulting therefrom may be obtained by urethroscopy, the x-ray, and renal function studies.

5. *Treatment.* The treatment of the condition is surgical and consists of the removal of the obstruction. This may be accomplished in certain cases by the passage of a sound with the forcible rupture of the valve; in certain other cases the obstruction may be removed by the urethrotome or by urethroscopic methods.

Of the operative procedures the selection of the suprapubic or perineal route will be governed by the personal preference of the operator. In infants and young children the suprapubic method has proved very satisfactory, the valvular obstruction being removed by its forcible rupture with a sound, its division with a rongeur, or its removal by scissors or cautery. In adults the condition is treated in most cases by intra-urethral methods.

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PLATES

PLATE 1

A step in the perineal operation for the removal of congenital valves of the posterior urethra. The posterior surface of the prostate has been freed of the levator muscle and the posterior layer of Denonvillier's fascia. Note outline of horse-shoe incision for exposure of the urethra. Insert shows flap of prostate with posterior wall of urethra drawn back exposing the valves.



PLATE 2

Final step in the perineal operation for the removal of congenital obstruction of the posterior urethra. The valves having been removed, the edges of the incision are approximated. Insert shows the completed line of suture.

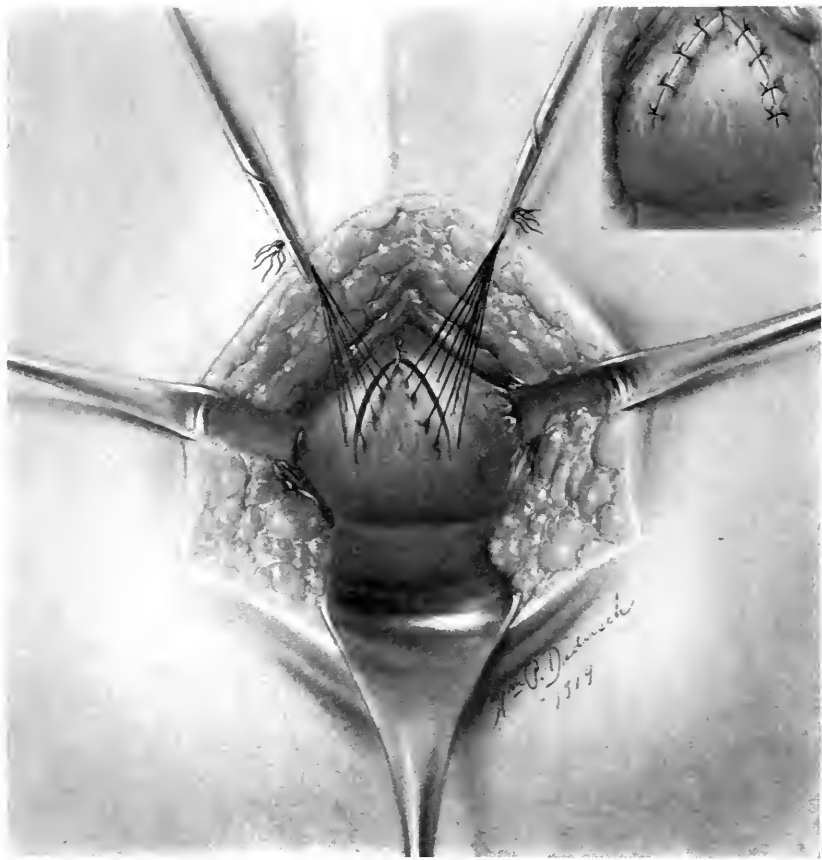


PLATE 3

Plate of specimen from case 1. Both valves arose from the bifurcation of the crista urethralis, a variety we have classified as type 1. Note the dilated posterior urethra, the hypertrophied bladder and the hydroureters.

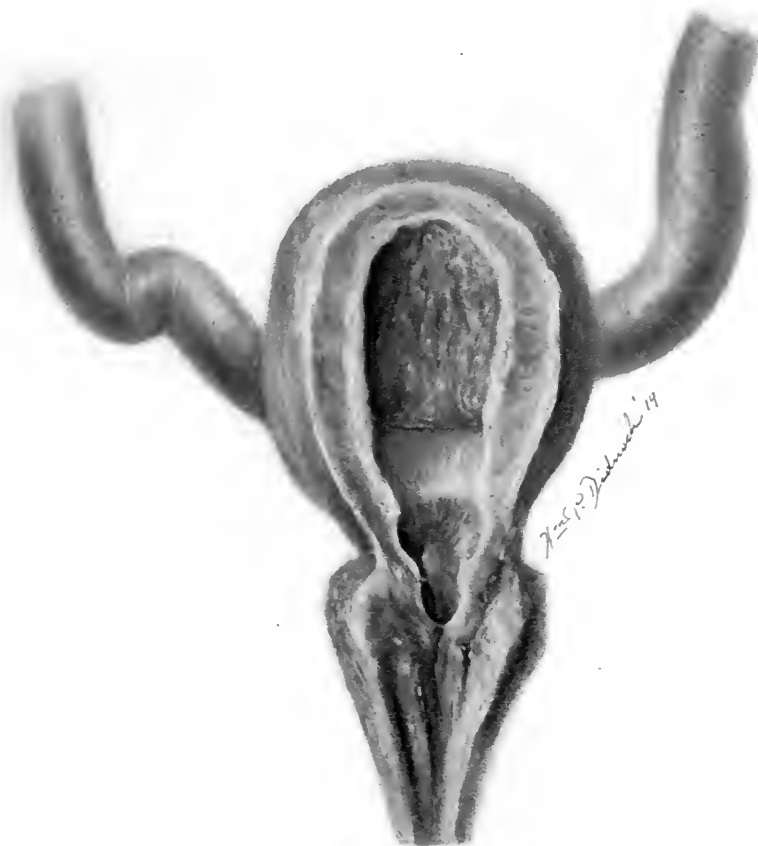


PLATE 4

Plate of specimen from case 4. An example of the crescentic type of valve (type 3), varieties of which may be found at any level of the posterior urethra. Note the dilated posterior urethra, the hypertrophied bladder and the hydro-ureters.

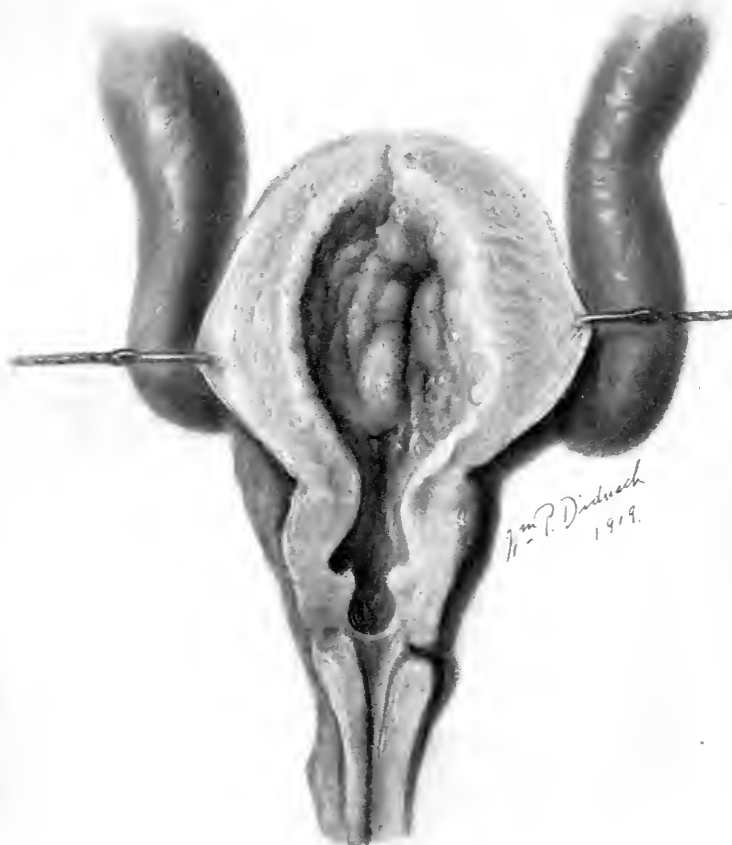


PLATE 5

Plate of specimen from case 10, showing the remains of congenital obstruction (type 2). Note the dilated bladder, the hydroureters and the bilateral hydro-nephrosis. The patient had been operated upon one year previously and the valves ruptured instrumentally. Insert shows dilatation of the sinus pocularis.



OBSERVATIONS ON CERTAIN RELATIONS BETWEEN SHELL FRACTURE OF THE SPINE AND CHANGES IN KIDNEY AND BLADDER FUNCTION *

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In reporting briefly this series of twenty cases of shell fracture of the spine as observed at the Walter Reed General Hospital, one must realize fully the lapse of time between the reception of the wound and our first clinical observation. During this period there took place a transition from the initial stage of spinal shock with complete retention of urine, to one of the three following conditions:

1. *Paradoxical, or passive incontinence*; in which examination reveals a full bladder. If the bladder be emptied by catheter, the incontinence will not recur until a certain amount of urine has reaccumulated. This is the type most frequently met in spinal injury and in cases of enlarged prostate.

2. *True incontinence*; in which the bladder empties itself spontaneously at intervals. This type is also known, technically, as periodic reflex micturition. Here, cerebral control only is lost and the bladder empties itself whenever a sufficient accumulation of urine induces the vesical reflex.

3. *Absolute incontinence*; sometimes called paralytic or complete incontinence, with loss of integrity in both sphincters. In such cases the urine constantly dribbles from the bladder, which, on catheterization, is usually found to be empty.

It was in these later stages, with their bewildering array of signs and symptoms that the cases first came to our attention, and it is on these phases only that we feel entitled to make comment.

* Read before the Section on Urology at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919, and published in abbreviated form in the Journal of the American Medical Association, Vol. 73, No. 21.

The cases were, in every instance, referred to the department of Urology from the Neuro-Surgical Section with a diagnosis of fracture of the spine and urinary incontinence.

The soldiers were all in the third decade, i.e., between twenty and thirty years of age, and none had a history of urinary incontinence prior to his wound. The time between injury and first observation averaged four and a half months. All cases gave a history of complete retention following injury, the mean average time of onset of incontinence being forty-eight hours. Each soldier had been catheterized while abroad; all of them were infected and most of them demanded catheterization as their right. Needless to say, it was on this assumption only that we took the liberty of doing simple cystoscopy on the bladders examined.

The site of lesion varied from the level of the sixth cervical vertebra to the cauda equina, the lumbar cord being the favored site in eleven cases, the dorsal in five, the cervical in three and the sacral in one. Several of these lesions overlapped from one section of the cord to another and in three instances the cauda equina and conus were secondarily involved.

Rectal involvement was general and ran a course symptomatically parallel to that of the bladder as we should expect from the innervation and developmental analogy of their respective sphincters. Sexual desire and ability were absent in all. None of the cases showed edema while observed.

Of this series fourteen of the cases were, after consultation, cystoscoped, every care being taken to preclude further infection, and with no untoward results. The picture was practically unvarying and the findings might be summed up in a composite group;

1. Normal or hypertonic contraction of the external sphincter.
2. Complete relaxation of the posterior urethra, the floor definitely falling away from the roof; the verumontanum is plainly seen, in most cases appearing to lie in the floor of the bladder. The internal sphincter is almost wholly obliterated as such, and the catheter draws water on passing the external sphincter muscle, just as it would in a case of tabetic bladder.

3. The trigone, in eight cases, was definitely atrophic in appearance, one case presenting a right lateral congestion, sharply demarcated in the mid line. Four cases gave a picture of raised trigone, the elevation being especially marked at the inter-ureteric ridge, and being rather apparent than real, due to the *bas fond* lying posterior to it.

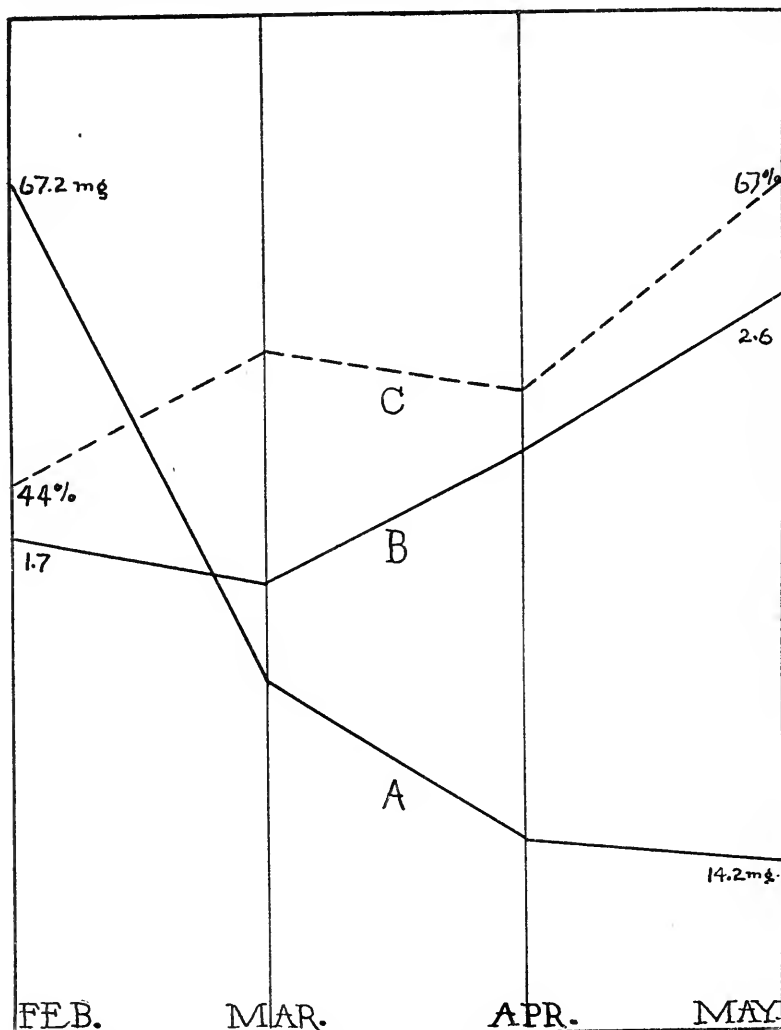
4. Generally speaking, the ureteral orifices are within range of normal, as to position, excursion and mobility.

5. Trabeculations were found in every case, gigantic in size, as a rule transverse and coarse on the floor, rather evenly distributed on the lateral walls, and having their greatest complexity on all the faces surrounding the vertex. It is probable that here the greatest local attempt at evacuation was made, as this is the site of distribution of the nervous plexus from the sacral autonomic supply, the anterior branch of the pelvic nerve. These trabeculations are strikingly coarse throughout in comparison with the lace-like, insular picture presented, according to Koll, by *tabes* in its incipient stage, and even, at times, after ataxia has first supervened, as we noted in three cases of *tabes* with beginning ataxia, examined in a collateral series. Only one case of diverticulitis was noted.

6. Nearly all the bladders had a general vaso-motor disturbance, particularly marked on the floor and chiefly characterized by irregular, ill-defined areas of venous congestion. This we should expect *a priori* from the work of Gaskell, Langley and Anderson, who showed that the motor nerves of the blood vessels of the entire body, the motor nerves of the sweat glands and of the internal vesical sphincter and posterior urethral muscles all belong to the same system. Consequently with a nervous lesion affecting the muscles adjacent to the bladder neck, we should expect an impairment of function, in whole or part, of the nerves controlling the vascular system as well as the sweat glands, and this we have noted to be the case. There was, however, no evidence of hematuria, and no case of trophic ulceration of the bladder.

7. The level of the lesion apparently had nothing to do, either with the functional activity of the bladder or the secreting

power of the kidney. The most marked instance of bladder disturbance was found in a case in which the lesion involved the 7th cervical and first three dorsal vertebrae only, and one of the mildest types of local involvement resulted from a lesion directly involving the lumbo-sacral cord.



A. Composite curve of fall of blood urea nitrogen. B. Curve of percentage relationship of first and second hour phenolsulphonphthalein. C. Relative upward curve of total phenolsulphonphthalein.

8. In one case only could we establish hyperidrosis on forcible distension of the bladder. In none of the other cases could we elicit a history of this sequence, though in all but one case there was a previous history of zonal hyperidrosis confined within the segmental limits of the thoracico-lumbar outflow, and always below the segment involved.

9. Each case presented residual urine in varying amounts, though there were times when some of them would give evidence of true incontinence, that is, a spontaneous emptying of the bladder, as soon as it had filled to a certain point. These same soldiers, however, would at other times, after an apparent evacuation, present as much as 250 cc. residual. It was very evident in watching them that the summation of stimuli necessary to establish a peripheral mass reflex is a variable quantity in any given patient, as well as in either of the three types of incontinence, after the incontinence has once been established. The residual urine as found varied from 0 cc. to 810 cc. with a mean average of 180 cc.

With the universal picture of residual urine present, even in those cases offering, at times, a picture of true incontinence, when the bladder spontaneously emptied itself, the possibility of back pressure was considered. Retention was studied through estimation of urea nitrogen, non-proteid nitrogen, creatinin and uric acid in the blood, and excretion by means of phenolsulphonphthalein, with examination of carefully collected twenty-four hour specimens of urine for urea nitrogen, sodium chloride, uric acid and creatinin in respect of milligrams per pound of body weight. The first series shows as follows:

Controls on a 1500 calorie diet at 135 pounds, averaged 12.5 mgm. urea nitrogen per 100 cc. plasma, with a non-proteid nitrogen of 38 mgm. The spinal cases exhibited a range of urea nitrogen from 13.8 in the lowest, which at that time appeared in excellent condition, and had a two hour phenolsulphonphthalein of 60 per cent plus 12 per cent, to 113 mgm. in the highest (nine times normal), with a bare trace of phenolsulphonphthalein; the mean average urea nitrogen of this series being 64.6 mgm., or about six times normal for the diet. Phenolsulphonphthalein determinations in this series of cases in this group showed a

lower output in the first hour than in the second, signifying a lack of facility on the part of the kidney quickly to take up function.

Creatinin in the blood stood at normal throughout, averaging 1.52 mgm. per 100 cc. We desire at this point to emphasize the fact that even in the very sick cases the blood creatinin stood at normal, the highest being 2.2 mgm.; this in spite of the previous wide excursions of urea nitrogen. The practical point to be borne in mind here is that, by the time creatinin has registered a serious rise in its curve, the patient is critically ill, whereas the urea nitrogen curve and the excretory function have long ago given the prognostic sign.

The cases were kept on practically the same food values for a month, given free access to water, and massaged over the whole body daily, especially over the region of the hypogastric and inferior mesenteric plexuses, with the triple idea of adding to the general tone of the organism, stimulating peripheral mass reflexes and expediting the vicarious compensatory activity of the skin for urea and uric acid. In the next series, one month later, the following results obtained:

Blood urea, lowest 11.98 mgm., highest 67.2; mean 26.82, or only twice normal. Creatinin averaged 1.1 mgm. In this series was a case of previous left nephrectomy with suprapubic drainage. This soldier was improving rapidly, had a urea nitrogen concentration of 13.8 (normal), creatinin normal, and a phenolsulphonphthalein output of 72 per cent, when suddenly his blood urea nitrogen increased to 67.2, his excretory function became practically nil, and he died with all signs of acute pyonephrosis and uremia. Aside from this adventitious circumstance the mean average urea nitrogen would be 23.71 mgm. The average phenolsulphonphthalein for this series was 60 per cent for two hours, the first hour averaging 37 per cent, the second 22 per cent, with a distinct tendency in all cases for the greater functional activity to take place during the first hour.

The third series of observations made still one month later, showed a blood urea concentration averaging 15.1 mgm. per 100 cc. plasma, the lowest being 8.2 in a patient clinically improving with a phenolsulphonphthalein of 61 plus 28, and the highest

being 32.6 with a phenolsulphonphthalein of 6 plus 9, equalling 15. The average phenolsulphonphthalein was 48 per cent, which included two very septic patients; aside from these the average would be 57 per cent, the average of the first hour being now appreciably increased over that of the second, except in the two who were still very sick.

The fourth series of observations made one month later, showed an average blood urea of 14.27 mgm., the highest being 31.6 mgm., the lowest 5.6 mgm. All of the phenolsulphonphthaleins here were distinctly improved as regards the relationship of the first and second hours, except in case X, which still had a blood urea of 31.6 mgm. and was not in good condition.

Throughout the series all cases were within range of normal as to blood sugar, and CO₂ tension in the blood, and the urines were persistently negative to reducing agent, even on forced carbohydrate diet.

We have then for our consideration a general picture of unusually high urea nitrogen, with high non-proteid nitrogen, and persistent normal creatinin in the blood, balanced by a comparatively low renal concentrating power for urea, with a low output of creatinin in twenty-four hours, and low uric acid output; and collaterally a colorimetric curve for phenolsulphonphthalein rising, as a whole, where the retention curve falls.

That there is not essentially a reciprocal curve existing between urea retention and phenolsulphonphthalein excretion would seem, however, to be borne out frequently in studying individual histories, though the number in this series is surely too small to form a basis for dogmatic statement. At one time the phenolsulphonphthalein curve rises more rapidly than the urea curve drops, and vice versa, but the curves always crossed sooner or later, and taken together gave an astonishingly good prognostic picture of the clinical change which later supervened, even though the curve changes have not always been synchronously reciprocal. Also in the stage of high urea retention, the renal function, where it appears fairly high in total, is as a rule lower the first hour than the second, which of course is an important point in interpretation.

It was at first assumed that the retention phenomena observed are habitually caused by back pressure leading to hydronephrosis. That this, at least is not universally true, was proved in one case in which we obtained autopsy. This soldier had 103 mgm. of urea nitrogen before death, and 68 mgm. of non-proteid nitrogen. His phenolsulphonphthalein was fairly high, 20 per cent and 45 per cent, but the first hour was less than half the second, and the appearance time was twenty-one minutes (gluteal). His average residual urine was 135 cc., with a relaxed bladder, and a bullet in the spine at the emanation level of the 9th, 10th, and 11th thoracics, which ought certainly to involve the ureters. Nevertheless, at autopsy there was found no evidence of hydro-ureters, or of hydronephrosis, as the specimens show. There was evidently here a distinct protective tendency manifested in the local compensatory activity of the bladder, although in this case the complete transection of the spinal cord had been clinically diagnosticated by a competent surgeon, while the soldier was in England, and the autopsy showed the posterior half of the cord completely shot away.

Another case in a collateral series of non-traumatic spines, showed at operation a giant-celled sarcoma, involving the lower dorsal and upper lumbar vertebrae. This case exhibited the same bladder picture described above, but there was no evidence of back pressure on the kidneys, his blood urea being 11.2 mgm. per 100 cc. of plasma, his non-proteid nitrogen 36.6 mgm., and his creatinin 1.2 mgm. It is to be noted here that, although the extraneous pressure was chronic in type, retention phenomena were not present. There was no evidence of tissue waste, no loss of body weight, and no hyperidrosis, though there was a distinct hyperesthesia of the peripheral blood vascular system. It is further to be noted that, though, there was a high residual urine he had no evidence of cystitis, not having been catheterized. This fact is not surprising. Sherrington as far back as 1900 wrote of a large series: "I have never seen cystitis ensue after transection in laboratory animals, though they were under observation many months."

This early tendency for the bladder to protect the upper tract may be explained by the work of Elliott, who found in

his decentralized bladders an overgrowth of musculature associated with an increase in the number of unstriated muscle fibers, as well as increase in the cross section of each fiber, associated with an increased suppleness and irritability of the muscle itself. This increased thickness of the bladder wall was observed many times at the operating table by Thompson Walker. In the one autopsied case in our series, this was also demonstrated and clinically we have noted a repeated tendency for the residual or contained urine to be greater than the capacity, showing a decided tendency on the part of the bladder to resist suddenly injected fluid.

From these observations we must assume the possibility of other causes than hydronephrosis for the retention phenomena exhibited, for otherwise the high nitrogen concentration would have been relieved by their previous catheter régime. The architectural incompetence of the kidneys to withstand long continued back pressure is recognized in the domain of prostatic obstruction, but here we are dealing with a sudden shock, with a tendency for the musculature of the lower tract to compensate quickly, and, at least, for many months to protect the higher tract. If hydronephrosis supervenes it certainly must be at a much later stage than in the cases we have observed. In addition to possible hydronephrosis we should be inclined to ascribe retention to several other potential factors.

In the cases, as first seen, the blood urea nitrogen was inordinately high; first, because of the tremendous tissue waste resulting from neurotrophism, as shown by diminished body weight and the general appearance of emaciation; secondly, these soldiers both while abroad, and in transit, were denied free access to water, in the attempt to keep away from too frequent catheterization, until, in most cases, they were all but completely dehydrated. Consequently with a low fluid content in the blood stream, the solid content would rise proportionately. Moreover, the neurotrophic hyperidrosis which takes place in practically all these cases, would further increase the concentration, and this augmented by the steady addition of tissue nitrogen, the whole being offset by a recalcitrance on the part of the kidneys to concentrate adequately for excretion (due to infection or

inhibition of neuropathic origin) would seem to explain satisfactorily the early retention phase. Certain it is that, given free access to water which the soldiers drank copiously at first, daily massage, and peripheral stimulation leading to the re-establishment of normal skin function, particular attention being given to stimulation of the hypogastric plexus, the picture changed markedly. The urea nitrogen and the non-proteid nitrogen decreased month by month, and the kidney excretory and concentrating capacity increased absolutely if not relatively for any given point of the curve.

The first retention is a shock phenomenon and undoubtedly involves both sphincters, the internal sphincter playing the dominant rôle. Later on the internal sphincter relaxes and the external sphincter takes up its compensatory hypertonic action. The problem is to evoke an automatic activity of the bladder at the earliest possible moment, and resolves itself down to an inhibition of this internal sphincteric hypertonicity. This shock phenomenon is probably due to the inhibiting action of the brain. Even a decentralized bladder will functionate on reception of nocuous stimuli, after cerebral inhibition is relaxed. This, as Head has shown, is due to a peripheral mass reflex, and as these spinal patients are all hyperesthetic, it may be effected in various ways, from stimulation of the plantar flexor spasm, to irritation of the prostatic plexus, the most direct approach, however, being anatomically by way of the hypogastric plexus. The first problem is to relax this tension by working backward from the periphery, and observations abroad by Young, Keyes, McCague, Beasley, Horra and others, has proved that this method has merit.

We are thus led to the following general conclusions:

1. Traumatic lesions of the spine produce the same picture in the bladder, regardless of the level of the lesion in the cord. This picture is the result of an acute shock myelitis, transverse in type, and the bladders involved differ in pattern and tonus from the bladders resulting from chronic longitudinal involvement of certain columns as seen in tabes, syringo-myelia, etc. The two types, however, present in common the same sequence of early retention followed by incontinence.

2. In these cases of the acute type, there is apt to be a very high content of blood nitrogen due to several factors, chief of which are increased katabolism, neuropathic inhibition of kidney function and renal infection.

3. In the cases in which the blood nitrogen remains high on forced hydration plus the establishment of true incontinence, we are led to believe that the persistent retention is not due to back pressure from hydronephrosis, but rather to renal infection. This fact should be of obvious interest in prostatic surgery.

4. Catheterization should not be resorted to, if it is possible to avoid it, as catheterization means sure infection, and it is to infection that these cases succumb.

Epicritical. It is aside from the province of this report to discuss at length the early care of these cases, though this is of much practical importance, as the same phenomena would undoubtedly arise in any case of spinal fracture from extraneous source.

We simply suggest, if possible, entire abstention from catheterization; for as has been proved many times, both clinically and experimentally, catheterization in neurotrophic lesions, means sure infection. Though Sherrington found no cystitis in his dogs, which were not catheterized, all of the dogs on which Goltz and Ewald performed bladder decentralization immediately developed cystitis, following catheterization, which was deliberately done in each case. The replacement fibrosis following renal infection is more dangerous to the patient than a permanent hydronephrosis, even granting a permanent hydronephrosis to exist (which we do not grant).

The clinical problem then is to foster the early establishment of incontinence without the passage of a catheter, as it is upon catheterization that infection primarily depends, and it is this infection rather than back pressure, which produces the real danger factor.

The first attempt should be made to establish immediate incontinence, even before debridement is done. To do this, both the internal and external sphincter must be relaxed, though the internal sphincter usually relaxes automatically after a few

hours. Being of smooth muscle, its relaxation might be expedited by the use of benzyl benzoate or acetate, hypodermatically, following the work of David I. Macht. The external sphincter is usually amenable to morphine, while the whole symptom complex may be ameliorated by working backward from the periphery, that is by careful, though persistent massage over the region of the hypogastric plexus.

If these methods fail, and intervention becomes inevitable, suprapubic aspiration with a needle is probably the best method of approach. Thompson Walker even goes so far as to say that open suprapubic cystotomy is preferable to the continued use of catheter, and surely the aspirating needle is less likely to infect than this latter method.

Strange to say, these bladders do not rupture, and as they are insensitive, no discomfort is experienced. The extent of their dilatation can be readily determined by inspection and percussion, and if, by judicious use of extravescical stimuli the onset of incontinence can be established early, without the use of catheter, the patient is further protected from the otherwise inevitable infection, which abroad, has resulted in a mortality of 50 per cent.

I wish to thank Captain Joseph M. Reed, Lieutenant Harry Wheelock and Lieutenant R. E. Cumming for their careful observations on these cases, and Lieutenant C. Henningsen of the Laboratory for chemical data obtained.

Following are epitomized histories of the cases observed:

Case 1

B. B., private, G, 120th Infantry Regiment, no. 25920, serial no. 198164. Age twenty-eight.

Previous history of incontinence negative.

Date of injury: 10-10-18.

Catheterized four times. Subsequent pressure over bladder to facilitate extrusion, during period of four weeks. Followed by use of inlying catheter to 11-28-18.

Onset of incontinence: Vague. 11-26-18 (?)

Lesion: 3d and 4th lumbar (?) X-ray, Casualty Clearing Station 41.

Operation: 10-10-18. Entrance through 5th lumbar; removed rifle bullet from "center of canal." B. H. no. 29.

Blood urea, Walter Reed General Hospital.

- 2- 7-19. 23.3 mgm. per 100 cc. plasma. Urea nitrogen.
2-10-19. 16.8 mgm. per 100 cc. plasma. Urea nitrogen.
3-25-19. 20.0 mgm. per 100 cc. plasma. Urea nitrogen.
4-18-19. 10.2 mgm. per 100 cc. plasma. Urea nitrogen.

Creatinin in blood:

- 3-25-19. 2.22 mgm. per 100 cc.
4-18-19. 1.2 mgm. per 100 cc.

Phenolsulphonphthalein:

- 2-18-19. 30 per cent first 70 minutes, 15 per cent second 60 minutes = 45 per cent.
3-26-19. 45 per cent first 70 minutes, 30 per cent second 60 minutes = 75 per cent.
4-18-19. 38 per cent first 70 minutes, 29 per cent second 60 minutes = 67 per cent.

Hemoglobin: 3-1-19. 70 per cent.*Blood count:*

- 3-21-19. W. B. C. 12,350. R. B. C. 3,261,000.
3-25-19. W. B. C. 11,200.

Cystoscopy: 2-8-19. Residual 200 cc.; capacity 420. Sensation on pressure present; expulsive force with cystoscope in situ, good. Internal sphincter relaxed completely, posterior urethra practically part of floor of bladder with verumontanum plainly seen with Brown-Buerger simple examining cystoscope; trigone atrophied; interureteric ridge not seen as such. Left ureteral orifice rather wide and gaping, right not seen. Fine trabeculations on the lateral walls—none on the floor.

Residual urine:

- 2- 8-19. 200 cc., cloudy, full of pus and colon bacilli.
3- 1-19. 150 cc.
3- 3-19. 375 cc.
4- 8-19. 530 cc. Heavy sediment of pus.
4-19-19. 370 cc. Slightly cloudy with pus.

Trophic ulcers: Right heel, small size, present 2-8-19.

Urine: Albumin trace; pus ++; casts negative; B. P. 135-110.

Rectal involvement: Yes.

Sexual powers: Absent; sexual desire absent.

Hyperidrosis: Extensive areas involved at times, notably for three days, about 3-13-19. No relation to fulness of bladder.

Clinical course: Generally good. Improving slowly.

Neurological findings: Motor. This is a root lesion, not a cord lesion, extending from cauda up to and including first lumbar. Left penis, left scrotum dead to tactile sense. Right perineal touch partially gone, all gone on left, showing conus involvement. Plantars, achilles and patellars all lacking.

Diagnosis: Root lesion including conus up to first lumbar inclusive, on left side.

Comment: This soldier was first seen four months after injury, at which time he had a definite paradoxical incontinence, with poor rectal control. There is no control of bladder, and practically no sensation, even on forced distension. Would come under the general head of automatic bladder. Note the difference in residual urine at various times, evidently due to irregular action of mass reflexes of which the patient is not aware at the time. The blood urea dropped from 23.3 mgm. to 10.2 mgm. in two months on same diet, during which time the phenolsulphonphthalein rose from 45 per cent to 75 per cent, creatinin remaining normal.

Case II

R. S., corporal, E, 48th Infantry Regiment, no. 24931, serial no. 2260123. Age twenty-two.

Date of injury: 10-31-18. Machine gun bullet 32 calibre still in spine. Previous history incontinence negative. Paralysis of both legs at once. Tingling and burning in feet and legs ever since.

Catheterized: For five weeks after injury, since which time has "emptied" freely and without control.

Incontinence (?)

Lesion: Bullet at level 11th dorsal; x-ray, Walter Reed General Hospital, 1-14-19.

Blood urea nitrogen:

2-4-19. 94.0 mgm. per 100 cc. plasma.

3-25-19. 19.5 mgm. per 100 cc. plasma.

4-19-19. 10.2 mgm. per 100 cc. plasma.

Blood creatinin:

3-25-19. 1.66 mgm. per 100 cc. plasma.

4-19-19. 0.90 mgm. per 100 cc. plasma.

Renal function:

2-18-19. 25 per cent + 10 per cent = 35 per cent, total 2 hours 10 minutes.

3-26-19. 20 per cent + 25 per cent = 45 per cent, total 2 hours 10 minutes.

4-19-19. 34 per cent + 10 per cent = 44 per cent, total 2 hours 10 minutes.

Blood pressure: 4-19-19. 110-65. Tycos auscultatory.

Hemoglobin: 3-3-19. 60 per cent.

Blood count:

1-24-19. W. B. C. 4800.

3- 3-19. W. B. C. 14,200.

Cystoscopy: Contraindicated.

Residual urine:

2-18-19. 160 cc. cloudy.

3- 1-19. 90 cc. cloudy.

4-19-19. 100 cc. cloudy.

Trophic ulcers: Right hip, right iliac crest; left hip, left iliac crest, right and left heels, sacrum, right and left knees mesially; all severe; the areas over both anterior superior spines being 20 by 10 cm.

Urine: Yellow, turbid, alkaline, 1018, albumin + + +, much mucus, no blood or casts. Triple phosphate crystals, and large amount of amorphous phosphates.

Rectal involvement: Yes. No sensation. Diarrhea.

Sexual powers: Nil.

Bladder: Urine collects in bladder for an hour or more, then passes without sensation of fulness or knowledge on the part of the patient. There is no sensation on forced distension nor is there any change in sensation on emptying.

Hyperidrosis: Continuous sweating body, and upper extremities; onset about 2-1-19. Five to six changes of pajamas nightly until recently. Examination 4-22-19, 9 p.m., moist over whole back, chest and abdomen; legs and feet dry. No relation to fulness of bladder according to statement.

Clinical course: Very sick patient.

Comment: This is paradoxical incontinence, but it is also a case of automatic bladder. Rising blood count probably due to infection from trophic ulcers, which grew steadily worse in spite of all care. Phenol-sulphonphthalein output rose slowly as urea decreased. The third series of function (44 per cent) is decidedly better than the second (45 per cent) because of the relative values in the first and second hours. Creatinin remains normal throughout up to 4-9-19. Patient slightly improving.

Case III

J. H. corporal, D, 362d Infantry Regiment, no. 24408, serial no. 2260123. Age thirty-one.

Previous history of incontinence negative.

Date of injury: 9-26-18. Argonne. Catheterized three or four times after wound. Incontinence began in two days. Unconscious after injury.

Lesion: Single plates 1-7-19 reveal no bony changes. Bullet wound on back to right of 8th dorsal. X-ray 2-1-19, hypertrophic caseous changes of 5th lumbar (old injury.) Gunshot wound 3d dorsal.

Blood urea nitrogen:

2- 4-19. 80.0 mgm. per 100 cc. plasma.

3-25-19. 15.8 mgm. per 100 cc. plasma.

4-23-19. 8.4 mgm. per 100 cc. plasma.

Blood creatinin: 3-25-19. 1.63 mgm. per 100 cc. plasma.

Renal function:

2-18-19. 15 per cent + 20 per cent = 35 per cent, 2 hours
10 minutes.

3-26-19. 55 per cent + 25 per cent = 80 per cent, 2 hours
10 minutes.

4-23-19. Not done account refusal patient; hyperirritability.

Hemoglobin: 3-3-19. 60 per cent.

Blood pressure: 3-26-19. 112-65. Tycos auscultatory.

Blood count: W. B. C. 7800.

Cystoscopy: Contraindicated.

Residual urine:

2-18-19. 210 cc.

3- 1-19. 60 cc.

Trophic ulcers: Back, left hip, both heels.

Urine: 2-24-19. Acid, 1028, albumin ++, triple phosphate crystals.

Rectal involvement: Slight control of rectum, for two or three minutes if stool is hard, but sphincter quickly fatigues.

Bladder: Was catheterized four times to his knowledge. Unconscious for unknown period of time after injury, does not know how many times he was catheterized in hiatus. Slight control: calls for bladder irrigation.

Sexual powers: Desire absent. No erections.

Hyperidrosis: Denies sweating up to 4-22-19. No sweating on fullness of bladder.

Clinical progress: Very poor 5-1-19.

Urine: Albumin trace, pus ++, no casts.

Blood pressure: 140-110. Tycos.

Comment: This is a case of hyperirritability, with general hyperesthesia. In this type of case where the peripheral involvement has an equal or greater signature than the central involvement, there is no sweating. Also this type have local registration of bladder and bowel distension reflex, and are not cases of true incontinence. Note rise in phenolsulphonphthalein both as to total and also as to hourly relationship compared with fall in urea nitrogen.

Case IV

C. G., private, M, 125th Infantry Regiment, no. 22700, serial no 264024. Age twenty-five.

Previous history of incontinence negative.

Date of injury: 6-18-18. Shrapnel. Not unconscious at any time.

Catheterization: Yes. Inlying till admission to Walter Reed General Hospital.

Onset of incontinence: Inlying catheter. Cannot tell.

Lesion: X-ray, Walter Reed General Hospital, 2-17-19. Fracture 12th rib, roughening of outline of 12th dorsal vertebrae. Diagnosis from department of neuro-surgery, complete transection myelitis cord; all sensation and motion below injury lost.

Blood urea nitrogen:

2- 4-19. 56.0 mgm. per 100 cc. plasma.

3-25-19. 19.0 mgm. per 100 cc. plasma.

4-21-19. 8.2 mgm. per 100 cc. plasma.

Creatinin: 3-25-19. 1.75 mgm. per 100 cc. plasma.

Renal function:

3-23-19. 30 per cent + 15 per cent = 45 per cent in 2 hours.
10 minutes (lumbar).

4-21-19. 61 per cent + 28 per cent = 89 per cent in 2 hours
10 minutes (deltoid) (probably got into a vein directly).

Blood pressure: 112-75. Tycos. 4-21-19.

Hemoglobin: 60 per cent.

Residual urine:

2- 4-19. 130 cc. Thick with pus.

4-21-19. 35 cc. Cloudy.

Urine: Albumin trace, pus cells fill field, casts 0, bacteria +, crystals 0, specific gravity 1018.

Cystoscopy: Contraindicated.

Trophic ulcers: Back lumbar, severe, right and left heels, medium severe.

Rectal involvement: Yes. Complete loss of power; diarrhea, mild chronic. Move daily without knowledge of the soldier.

Sexual powers: Desire absent. Throughout course of case has had erections which are unattended by libido. These erections are particularly quick in reaction, at times when he is being bathed. See comments.

Bladder: Was treated a'demeure—from beginning—but with catheter now out (on massage), he has no sensation of fulness in bladder. It fills up and overflows. Is not sensitive to nocuous stimuli. There is no sensation whatever in penis or scrotum. Both dribbling and automatic facilitation are without the soldier's knowledge.

Hyperidrosis: Since injury always dry and cold. Remembers this distinctly because it was noticeable by absence. Since removal of inlying catheter has not sweated even with full bladder.

Clinical progress: Poor.

Comment: 5-4-19. Note the rise in the phenolsulphonphthalein output as the blood urea decreases. The absence of hyperidrosis is anomalous. In a case of irritable reflex activity one might expect this phenomenon to supervene for a period up to three months, but this is a case of transverse involvement, and is classified under the type of "automatic bladder" in which type we should ordinarily expect hyperidrosis to be manifest.

Note the erectile power without other sensation, or pain on fulness of bladder; a result of mass reflex from innocuous stimulation. The phenolsulphonphthalein output of 61 per cent + 28 per cent is explained by evidently getting not only the needle into a vein, but probably fully half the 6 mgm. of the dye got in the vein. This not only decreased appearance time, but greatly added to the total value of the first hour and also made the relative difference between the first and second hours greater. The true facts here would best be expressed by 40 + 20, but there is, however, a distinct improvement as the urea decreases.

Case V

T. W. Major, Medical Corp, 18th Infantry Regiment, no. 22700, serial none. Age twenty-six.

Previous history of incontinence none.

Date of injury: 10-9-18. Missile passed through left kidney, upper pole.

Catheterization: To date from 10-9-18.

Onset of incontinence: Four weeks after injury according to statement.

Lesion: Line of 1st and 2d lumbar. X-ray (?). Not completely paralyzed.

Operation: October 30, 1918. Debridement, since which there has persisted a urinary sinus left 11th interspace, post axillary line. No improvement followed. Intense burning and hyperesthesia of soles of feet, which followed injury, are worse since operation. Practically clear urine comes from the sinus. At times as much as 100 cc. can be expressed by abdominal pressure, at others, none can be recovered. He is too sick to operate on again at present. Thorium nitrate injected into sinus shows a circumscribed circular area size of a dollar at level of upper pole left kidney. (Unsatisfactory.)

Blood urea nitrogen:

2-12-19. 15.4 mgm. per 100 cc. plasma.

3-25-19. 26.6 mgm. per 100 cc. plasma. (48 non-protein N.)

Creatinin: 3-25-19. 1.3 mgm. per 100 cc. plasma.

Renal function: 3-25-19. 5 per cent + 15 per cent = 20 per cent.

Hemoglobin: 3-3-19. 55 per cent.

Blood count: 3-3-19. 11,000 W. B. C.; 3-25-19, 11,150 W. B. C.

Cystoscopy: 4-7-19. Entrance with difficulty to post-montanal sulcus, recovery of 370 cc. of urine thick with pus. Capacity 300 cc. forced distension, at which time patient complains of great irritation and begins to sweat profusely. Also great increase in plantar hyperesthesia. Prostatic outline entirely absent. Trigone atrophied, posterior urethra definitely part of bladder; verumontanum plainly seen with ordinary cystoscope at great distance from lens. Deep post-montanal bassinet. The ureteral orifices are difficult to find as the trigonal cornua are lost in trabecular formations with beginning diverticula in which the orifices are evidently hidden. Heavy trabeculations over apex and roof, and fine trabeculations everywhere on lateral walls, but none on the floor. Only mild evidence of cystitis.

Residual urine: 3-13-19. 350 cc. Cloudy pus.

Trophic ulcers: None.

Rectal involvement: Yes. Control absent, but though involuntary, he is aware of desire to defecate.

Bladder: Distension of bladder noted as painful always, and accompanied by marked burning in urethra. Forced distension accompanied by marked hyperidrosis of body, not involving feet.

Sexual powers: Absent entirely as to desire and erectile power.

Hyperidrosis: Yes, especially on forced distension of bladder, when he breaks out in profuse general perspiration not involving the feet. At other times there is fairly marked hyperidrosis over lower abdomen and around the genitalia and on the legs to the knees. This has begun since he came to the hospital.

Urine: Turbid, alkaline, albumin +, field obscured by pus cells. No casts. Many colon bacilli.

Blood pressure: 140-95.

Clinical course: Poor. Patient is retaining retroperitoneal pus. Has been decided to transfer him to base nearer home, without operation.

Comment: This soldier is not an automatic bladder case. In this case the missile evidently grazed the bony spine, and in addition to partially destroying temporarily the reflex arc, set up a hyperirritable condition of the peripheral nerves. There was evidently a urinary pouch formed in the left flank, with dissection along the left ureter, across the top of the bladder and up along the urachus and it was the pressure from without that caused the frequent desire to be catheterized (q. six hours) coupled with great irritability of the posterior urethra. He was too sick to operate on, but he should have had abdominal drainage under local anesthesia. The persistence of high urea here in spite of free drainage points to infection of the other kidney.

Case VI

R. O., private, E, 9th Infantry Regiment, serial no. 293922. Age twenty-nine.

Previous history of incontinence negative.

Date of injury: 9-14-19. Struck with shrapnel right hip, and almost immediately thereafter with rifle ball which entered about 10th dorsal.

Catheterization: None, according to statement (?).

Onset of incontinence: Two days from time of injury. Constant dribbling.

Lesion: 7th, 8th, and 9th spinal vertebrae

Operation: Evacuation Hospital no. 1, 9-14-18. Diagnosis, gunshot wound, battle, penetrating lumbar region posteriorly severing spinal cord, wound debrided and closed.

Blood urea nitrogen: 2-4-19. 103 mgm. per 100 cc. plasma.

Renal function: 2-18-19. 20 per cent + 45 per cent = 65 per cent.

Cystoscopy: Not done. Died 2-28-19.

Residual urine: 2-18-19. 135 cc. cloudy.

Urine: 1-5-19. Alkaline, specific gravity 1012, albumin trace, sugar and acetone negative, occasional red cells, no cast, many pus cells.

Blood count: 1-3-19. W. B. C. 10,000.

Trophic ulcers: Report from base no. 23, 9-20-18. Both feet, legs, left hip and buttocks. Base no. 8, 10-23-18, large suppurating wound on back, iliosacral and gluteal regions gangrenous. Deep suppurating ulcers right hip.

Rectal involvement: Yes. Involuntary and without knowledge of soldier.

Bladder: Report from Base no. 26, 9-20-18, says there was retention of urine; catheterized twice daily. This was evidently for residual urine and not complete retention.

Sexual powers: Desire and ability absent since injury.

Hyperidrosis: No history.

Died: 2-18-29. Diagnosis: Asthenia.

Pathological report: Anatomic diagnosis: Emaciation. Kidneys: fatty and parenchymatous changes especially the left. Liver: passive congestion marked. Traumatic injury, spinal cord, lower dorsal region. Healed wounds, multiple, posterior surface of body, also sacral, calcaneal and other lesser decubiti. Pleuritis, chronic adhesive, right. Hydro-pericardium, slight.

Clinical diagnosis: Gunshot wound penetrating lumbar region posteriorly severing cord (spinal), 7th and 8th vertebrae injured. Paralysis, lower extremities, bladder and rectum. Paraplegia. Multiple decubiti.

Objective symptoms: Condition on admission, poorly nourished and paralytic; general condition, weak and anemic. Loss of sensation, pain, touch and temperature, both legs and thighs. Extensive decubitus ulcer over sacrum and coccyx. Abdomen flat. Complete paralysis of both lower extremities; loss of sphincter control of bladder and rectum. Linear scar 8 inches long to left of mid line extending downwards from 4th dorsal vertebrae; also scar $\frac{1}{2}$ inch long 2 inches to left of mid line, level of 7th dorsal vertebra. Both knee joints, flail. Kidneys—Left kidney, 150 grams, 110 by 60 by 30 mm. External, normal; moderate

fetal lobulation. On section, cut without increased resistance. Capsule strips readily leaving smooth surface presenting conspicuous stellate veins. Cortex, 5 to 7 mm.; cortex and pyramids, fairly well differentiated; blood vessels, in place, rather conspicuous but as a whole, section reveals exceedingly pale, grayish yellow tissue. Pelvis appears normal.

Right kidney, 145 grams; 110 by 60 by 30 mm. External, essentially normal; color, pinkish gray, much darker in general aspect than opposite kidney; like opposite kidney, moderate fetal lobulation present. On section, cuts with normal resistance; capsule strips readily, leaving smooth surface in which stellate veins are conspicuous. Cortex 5 to 7 mm.; cortex and pyramids, fairly well differentiated, much better than in opposite kidney.

Adrenals: Adrenal bodies appear normal.

Bladder, etc.: Bladder, much contracted; contains 15 cc. fluid resembling pus. On section, walls thickened; mucosa, in centre, dull reddish brown and everywhere appears congested. Ureteral ridges, swollen and very conspicuous, left one deep red; right one covered by thin calcareous incrustation, 0.5 mm. in thickness; beneath this incrustation, ureteral ridge dull yellowish gray. Prostate gland, normal; measures anteroposteriorly, 30 mm. and laterally, 25 mm. Penis normal; prepuce lacking (surgical removal). Testicles feel and appear normal.

Spinal cord: 7th and 8th dorsal vertebrae, lack spinous processes and laminae; spinal canal at this point bridged by connective tissue. In cord, lower dorsal region, just above lumbar enlargement, a cyst-like structure, 20 by 16 mm., posteriorly, immediately beneath region deficient in bony covering, which seems to extend about half way through cord; extending through upper part of cyst, two spicules of bone, one on each side which apparently pierces cord nearly to anterior surface. In region below this cyst-like body, dura is firmly adherent to canal so that cord is removed with difficulty; slight gelatinous exudation in canal but it does not appear infected. Cord immediately below cyst-like portion, very narrow and apparently atrophied.

Bacteriological findings: Cultures from gall bladder, no growth. Culture from heart's blood, a small, pleomorphic, Gram-positive, hemolytic bacillus; 50 to 100 organisms per cubic centimeter.

Histology: Adrenals: No marked pathologic change. A few areas with vessels much distended with red blood cells. Kidneys: Glomerular capsules thickened, epithelium appears swollen; very rarely a glomer-

ulus has lost its essential characteristics and appears to be undergoing fibroid changes. Tubules are usually widely separated, intervening space filled with scattered small round cells, some fibroblasts and loose connective tissue; walls of blood vessels are not thickened. Cells of tubules granular with well staining nuclei. Very rarely a small collection of mononuclear round cells found. Chronic parenchymatous nephritis.

Clinical course: Died.

Comment: This case had an involvement of the thoracic spine with imbedding of bullet as demonstrated at autopsy in the very level where one would expect involvement of the ureters with dilatation and secondary hydropyonephrosis from regurgitant ureteritis. Also from the history obtained from Base no. 26 it would seem that at one time there must have been considerable back pressure. He had a blood urea of 103 mgm. per 100 cc., but his phenolsulphonphthalein output within ten days of death was 65 per cent for two hours and ten minutes, with an appearance time of twenty-one minutes, pointing to a parenchymatous type of involvement. The bladder is mildly typical of the kind we are describing, with dilatation of the posterior urethra, universal trabeculation, etc., and yet there was no evidence of hydroureter, and no sign of hydronephrosis, or of pyonephrosis present, even with a practical transection myelitis at the region of the 9th dorsal. This proves that high blood urea at least does not necessarily prove hydronephrosis, and that retention, with involvement of the lower thoracic spine is not necessarily accompanied by hydroureter and hydronephrosis. Possibly if this patient had lived he might later have had a hydronephrosis, but even at this stage he had all the clinical findings assumed to lead to this condition, with negative autopsy.

Case VII

O'C. J. W., Private, D. 26th Infantry Regiment, No. 22710. Age twenty-seven.

Previous history of incontinence.

Date of injury: 7-21-18. Soissons.

Catheterization: For three days after according to statement. Following this could force water out at will.

Onset of incontinence: Three months after injury, dribbling. Later retained diurnal control, but nocturnal dribbling has continued to present.

Lesion: 4th and 5th lumbar.

Operation: On field within twenty-four hours. Failure. Later Base no. 202 removed fragment of shell from 4th and 5th lumbar.

Blood urea:

2- 4-19. 48.0 mgm. per 100 cc. plasma.

3-25-19. 26.3 mgm. per 100 cc. plasma (45.8 mgm. non-protein N.).

4-25-19. 15.8 mgm. per 100 cc. plasma.

Creatinin: 3-25-19. 1.1 mgm. per 100 cc. plasma.

Renal function:

2-18-19. 50 per cent + 25 per cent = 75 per cent (lumbar).

4-24-19. 42 per cent + 17 per cent = 59 per cent (gluteal).

Blood pressure: 4-24-19. 120-65. Tycos auscultatory.

Cystoscopy: 4-2-19. Residual plus one hour, 430 cc. Could not void. Capacity 600 cc. Clear, third washing. Posterior urethra relaxed; irregular trabeculation both lateral walls. Trigone atrophied. Right ureteral orifice gaping, rigid; verumontanum seen in floor of urethra, with the muscle of Bell clearly differentiated from surrounding mucosa.

Residual urine:

2-18-19. 810 cc. in one-half hour. Pus + + +.

4- 1-19. 180 cc. Cloudy.

4-24-19. 555 cc. Clear.

Trophic ulcers: Healed over sacrum 8-4-18.

Rectal involvement: Yes. No sensation when bowels are moving.

Bladder: Feels bladder when full. Dribbles at night only. Control in day.

Sexual powers: No desire or ability.

Pain; Pain in plantar region (good sign). Feels like needles sticking.

Hyperidrosis: Onset since injury. Skin moist during day, but sweating particularly marked at night. Would awaken one to three hours after going to sleep, very wet, necessitating change of nightwear. Improvement 4-22-19. Hands moist. Feet always cold, but socks moist. Apparently no relation to fullness of bladder.

Clinical progress: Fairly good.

Comment: This lesion was fairly low down, and in spite of the partial break in the reflex arc, his diaphragm and abdominal muscles were undoubtedly able to partially overcome the reflex action of the bladder expelling some water but not completely emptying the bladder. This is not an automatic bladder.

There is not here a relative rise in phenolsulphonphthalein with decrease in urea but all values are so near normal that the changes are only variations of the normal.

Case VIII

A. K., private, Machine Gun Company, 119th Infantry Regiment, no. 25918, serial no. 1999837. Age twenty-three.

Previous history of incontinence negative.

Date of injury: 9-29-18.

Lesion: Fracture upper edge left ilium and 5th lumbar vertebra.

Operation: 10-22-18. Laminectomy; spinous processes 5th lumbar and 1st sacral. Pus in spinal canal. Two months later sensation began to appear, below the injury.

Catheterization: Not for several days after injury.

Blood urea N.:

2-10-19. 26.5 mgm. per 100 cc. plasma.

4-11-19. 12.8 mgm. per 100 cc. plasma.

Creatinin: 4-17-19. 1.0 mgm. per 100 cc. plasma.

Renal function:

3-26-19. 50 per cent + 35 per cent = 85 per cent, 2 hours 10 minutes (deltoid).

4-17-19. 50 per cent + 22 per cent = 72 per cent, 2 hours 10 minutes (deltoid).

Blood pressure: 4-17-19. 140-75. Tycos auscultatory.

Residual urine:

2-19-19. 75 cc.

3-31-19. 215 cc.

4-17-19. 55 cc.

Hemoglobin: 3-3-19. 65 per cent. R. B. C. 13,000.

Cystoscopy: 3-31-19. Residual urine 215 cc. Capacity 270 cc. Posterior urethra relaxed. Coarse trabeculations floor and both lateral walls. Diverticulum on floor 1 cm. behind normal position inter-ureteric ridge midaxis. Two phosphate stones lying in floor centre, respectively $\frac{1}{2}$ by $\frac{1}{2}$ by $\frac{1}{2}$ cm. and $\frac{1}{3}$ by $\frac{1}{3}$ by $\frac{1}{3}$ cm. Muscle of Bell clearly outlined. Trigone atrophied at least in appearance. Both ureteral orifices dilated, apparently rigid. Verumontanum seen, floor of bladder, mid line, relatively prominent. This is typical of bladder often ascribed to early tabes.

Trophic ulcers: None.

Rectal involvement: Yes, but not marked. Can control unless diarrhea is present.

Bladder: This patient was not catheterized for several days after the injury, then began to dribble and catheter was evidently used to drain residual urine. Distension of this bladder causes distress, and slight sweating on forehead and palms. He now has incontinence every five to ten minutes and wears a Chetwood clamp to protect himself.

Pain: None, sensation.

Sexual power: Has desire and erectile power; also nocturnal emissions.

Hyperidrosis: Onset 2-10-19. Feet and legs have always sweat since onset. Lately axillae sweat, since he has been out of bed. Distension of bladder causes some distress and sweating of palms and forehead.

Urine: 3-23-19. Alkaline, 1012, cloudy, albumin trace faint, sugar and acetone negative; many pus cells and triple phosphates.

Clinical progress: Rectal control better, sexual ability returning, bladder control slightly improved, though still wears Chetwood clamp. Complains of weakness of right ankle. General health good.

Comment: This case could have been saved the use of the catheter, though it apparently has not materially affected the outcome.

Case IX

J. B. Second lieutenant, 118th Infantry Regulars, no. 25601. Age thirty.

Previous history of incontinence negative.

Date of injury: 10-17-18. High explosive tore left leg off 5 inches below knee. Foreign lodgment in spine.

Catheterization: Two days after injury, as soon as he got to Base Hospital; was never unconscious as far as he knows. Inlying catheter in six weeks. Followed by incontinence which continues.

Onset of incontinence: Probably at once.

Lesion: Gun shot wound first lumbar. No x-ray. Laminectomy 10-19-18.

Blood urea nitrogen:

2- 4-19. 105 mgm. per 100 cc. plasma.

3-25-19. 21.0 mgm. per 100 cc. plasma.

4-24-19. 16.0 mgm. per 100 cc. plasma.

Creatinin:

3-25-19. 1.0 mgm. per 100 cc. plasma.

4-23-19. 1.3 mgm. per 100 cc. plasma.

Renal function:

4- 1-19. 22 per cent + 15 per cent = 37 per cent.

4-24-19. 19 per cent + 22 per cent = 41 per cent.

Blood pressure: 135-95. Tycos auscultatory.

Cystoscopy: 1-27-19. No residual. Capacity 100 cc. Trabeculations both lateral walls. Both ureteral orifices rather unduly dilated, but there is some excursion of the trigone extension. Posterior urethra only slightly dilated at the internal spincter. Verumontanum cannot be seen. Trigone not elevated. Bladder tone good. This is a case of true incontinence as seen at this time, beginning varies with paradoxical incontinence.

Residual urine:

3-25-19. 0 cc. (cystoscopy).

4- 1-19. 250 cc. fairly clear.

4-24-19. 130 cc. in one hour. Slightly cloudy.

Hemoglobin:

3- 3-19. 75 per cent. W. B. C. 8000.

3-21-19. 85 per cent. W. B. C. 9625, R. B. C. 4,872,000.

3-25-19. W. B. C. 11,500.

Rectal involvement: Never had control, but has knowledge now when they move, but only as they are moving.

Sexual powers: Nil.

Hyperidrosis: Onset at once. Hot to waistline with perspiration over abdomen and back and legs to knees. Lower legs and feet cold. Sweating apparently has nothing to do with fullness of the bladder.

Clinical progress: Improving.

Comment: This case is passing from the stage of paradoxical to true incontinence. Time of transition, seven months.

Case X

McI. L., first lieutenant, K, 309th Infantry Regulars, no. 25062, serial no. 1173172. Age twenty-seven.

Previous history of incontinence negative.

Date of injury: 7-18-18.

Catheterization: None.

Onset of incontinence: At once.

Lesion: 7th cervical and 1st to 4th dorsal.

Operation: 10-19-18.

Blood urea nitrogen:

2- 4-19. 113 mgm. per 100 cc. plasma.

3-25-19. 28.4 mgm. per 100 cc. plasma.

4-24-19. 32.6 mgm. per 100 cc. plasma.

Creatinin: 3-25-19. 2.0 mgm. per 100 cc. plasma.

Renal function:

3-25-19. 3 per cent, 2 hours and 10 minutes.

4-24-19. 6 per cent + 9 per cent = 15 per cent.

Blood pressure: 4-24-19. 165-110. Tycos auscultatory.

Residual urine:

1-27-19. 375 cc.

4-24-19. 175 cc.

Cystoscopy: 1-27-19. Residual urine 375 cc. After this was withdrawn, bladder resists forcibly 225 cc. distension. Much washing necessary to clear bladder of detritus and pus. Mild catarrhal cystitis throughout. Pain sense lacking in bladder on distension, but patient can tell the difference between hot and cold water injected. Beginning diverticulum on floor midline 1 cm. behind interureteric ridge. Cathedral vaulting throughout. Trigone slightly congested in center. Roof particularly trabeculated. Prostatic outline in range of normal. No relaxation of posterior urethra.

Bladder: Emptied by pressure over lower abdomen for first three weeks after injury, then up to 2-1-19, dribbled a few drops at a time without knowledge of patient. Since being cystoscoped and washed at Walter Reed General Hospital, he has sensation and desire to urinate at times, evidently verumontanal irritation increased; has, 5-1-19, ability to hold water three or four minutes after desire to empty is manifest.

Renal function:

4-16-19. 20 per cent + 15 per cent = 35 per cent.

4-23-19. 13 per cent + 6 per cent = 19 per cent. Patient was very sick at this time and showed every sign of absorption from right kidney.

Residual urine: 4-23-19. 130 cc. Cloudy, albumin, pus and colon bacilli.

Cystoscopy: 12-1-18. Base Hospital No. 14. Trabeculations, definite pouch behind trigone, dilatation internal sphincter, verumontanum seen with concave cystoscope. (Report)

Trophic ulcers: 4-5-19. Healed area on sacrum, which was from appearance a large deep sore.

Rectum: No control till 12-24-18, when he was able to control and defecate normally.

Hyperidrosis: Onset at date of injury, 11-8-18. Profuse perspiration, whole left side of body, including face, arms, trunk and leg to foot. Says he sweats all the time and this is confirmed by our observations.

Clinical progress: Poor.

Neurological diagnosis: Lesion of conus. Patellar reflexes present; achilles lacking.

Urine: Albumin trace, pus ++, no casts.

Blood pressure: 135-100.

Comment: This soldier had an acute pyonephrosis, right which was operated before admission to Walter Reed General Hospital. Since operation the wound has been foul and sloughing, and the soldier does not seem to be able to recover from absorption process. His general condition to date makes operation of further magnitude dangerous. His blood urea is not seriously high. The phenolsulphonphthalein output is much more in accord with his general clinical condition.

Case XIV

G. G., sergeant, C, 28th Infantry Regiment, no. 23867. Age twenty six.

Previous history of incontinence negative.

Date of injury: 7-18-18.

Onset of incontinence: At once; gradual improvement.

Lesion: 2d lumbar.

Operation: France, 7-21-18. Debridement.

Blood urea:

2- 4-19. 93.0 mgm. per 100 cc. plasma.

4-16-19. 21.4 mgm. per 100 cc. plasma.

4-22-19. 8.4 mgm. per 100 cc. plasma.

Creatinin: 4-16-18. 0.7 mgm. per 100 cc. plasma.

Renal function: 4-22-19. 41 per cent + 18 per cent = 59 per cent, 2 hours 10 minutes.

Residual urine: 4-22-19. 20 cc. Cloudy with shreds.

Cystoscopy: Not done.

Tropic ulcers: None.

Hyperidrosis: After injury general sweating, continuous, especially marked during sleeping hours. Did not involve face and arms (?).

Clinical progress: Good.

Case XV

O. G., corporal, K, 6th Infantry Regiment, no. 28040, serial No. 733731. Age twenty-three.

Previous history of incontinence negative. Admitted Walter Reed General Hospital 4-8-19.

Date of injury: 11-10-18.

Catheterization: For one month after injury.

Onset of incontinence: Retention for twenty-four hours. Then catheterized once daily for one month. Incontinence then and control 4-22-19, except on laughing, coughing or sudden motion.

Lesion: 4th and 5th lumbar.

Blood urea:

4-15-19. 11.98 mgm. per 100 cc. plasma.

4-22-19. 22.1 mgm. per 100 cc. plasma.

Creatinin:

4-15-19. 1.30 mgm. per 100 cc. plasma.

4-22-19. 1.35 mgm. per 100 cc. plasma.

Renal function: 5-5-19. Entrance effected with difficulty, No. 18 Wappler concave examining cystoscope. Says he feels the cystoscope in the bladder. Capacity 250 cc.; residual urine 250 cc. Detrusor action strong. Heavy horizontal trabeculations on the floor, lighter horizontal ones on lateral walls, and arborescent, interlocking trabeculations around the apex. Trigone flatter than normal, interureteric ridge practically obliterated. Internal sphincter falls away from cystoscope, posterior urethra forms part of floor; verumontanum plainly seen. Many cellules. No diverticula, no stone.

Trophic ulcers: One small one lower sacral area one month after wound. Healed.

Hyperidrosis: Feet, ankles, lower legs, have sweat all the time since wound, never before.

Rectum: First movement five days after wound by enema. No sensation as to fulness of lower bowel. Can control formed stool, but not liquid one.

Sexual powers: Ability and desire—negative.

Sensations: Burning right foot (good sign.)

Bladder: Unable to micturate at first. Was catheterized about twenty-four hours after injury en route to Base. Had sensation of pain when bladder was full. No incontinence for one month when catheter was discontinued.

Neurological findings: Areas of anesthesia in both legs—connoting root lesion up to 2d lumbar. Conus and cauda equina involved. Numb all over perineum and sacrum. Testicular sensation not lost, though hyperesthetic. This means conus lesion which will probably not improve. No ankle jerk or plantar response either side.

Comment: This is not an automatic bladder case. Epididymitis six months ago. Recurred after cystoscopy at this station. He is generally improving, and aside from his gait is well.

Case XVI

V. DeB., private, Headquarters Company, 308th Infantry Regiment no. 28153.

Previous history of incontinence negative.

Date of injury: 9-14-18.

Catheterization: Complete retention. Catheterized three times first twenty-four hours after injury.

Onset of incontinence: Twenty-four hours after injury. Regained complete control in two weeks.

Lesion: 2d lumbar vertebra.

Operation: 9-15-18. Debridement. Bullet removed with loose bone fragments.

Blood urea: 4-23-19. 9.32 mgm. per 100 cc. blood plasma.

Creatinin: 4-23-19. 1.10 mgm. per 100 cc. blood plasma.

Renal function: 4-23-19. 42 per cent + 16 per cent = 58 per cent, 2 hours 10 minutes.

Residual urine: 4-23-19. 115 cc.

Cystoscopy: Not done.

Trophic ulcers: None.

Rectum: At first loss of control entirely for twenty-four hours.

Sexual powers: Normal.

Hyperidrosis: Profuse since injury, especially legs and feet. Has gradually improved with improvement in other signs and symptoms.

Clinical progress: Good.

Comment: This case was admitted late in the series and a long time, seven months, has elapsed since injury.

Case XVII

L. T. S., M.A., 145th Infantry, register no. 26661. Age twenty-five. Previous history of incontinence negative.

Date of injury: 9-28-18.

Catheterization: Never.

Onset of incontinence: Forty-eight hours after injury approximately.

Lesion: 12th dorsal and 1st, 2d, and 3d lumbar. X-ray, Walter Reed General Hospital, 2-28-19.

Operation: 10-2-18, France. Debridement.

Blood urea: 5-1-19. 14.2 mgm. per 100 cc. plasma.

Creatinin: 5-1-19. 1.52 mgm. per 100 cc. plasma.

Renal function: 37 per cent + 17 per cent = 54 per cent, 2 hours 10 minutes.

Cystoscopy: 4-26-19. Could not urinate. Contained urine 560 cc. Clear. Capacity under distension 600 cc. Trabeculations large on the floor, walls and roof free. Both ureteral orifices normal and normally placed with normal excursions. Slight edema of the prostate. Slight dilatation only of the prostatic orifice, only slight enlargement of the post montanal space. Verumontanum not seen. (Left acute epididymitis following cystoscopy.)

Trophic ulcers: None.

Hyperidrosis: None at any time according to statement.

Rectal involvement: Has practically parallel course with bladder history. At first obstipation, then incontinence. Now has good control.

Sexual powers: Absent.

Progress: Good.

Comment: This injury did not directly involve the medullary portion. Debridement effected relief of pressure and patient has improved ever since. He now walks easily and his sensation is returning, also knee jerks, which are the last to return. He was admitted too late for a seriatim study of his retention values. At the time of first observation he was well on the road to recovery. It is of interest in these cases that are recovering to note the persistence of the bladder figure.

Case XVIII

G. R. N. Age twenty-four.

Incontinence: None at any time.

Date of lesion: 10-9-18.

Location of fracture: Injury to 2d, 3d, and 4th cervical vertebrae, with partial loss of substance. No injury to cord. Missile entered right cheek, struck spine and emerged into throat. Sequestra removed from post-pharyngeal wall.

Blood urea: 8-8-19. 15 mgm. per 100 cc.

Creatinin: 8-8-19. 1.6 mgm. per 100 cc.

Gross phenolsulphonphthalein: 8-8-19. 55 per cent in two hours.

Cystoscopy: Patient unable to void just prior to examination. Shows marked general hyperidrosis throughout examination. No. 18 Wappler cystoscope entered with ease after anesthesia with novocaine 4 per cent. Contained urine—350 cc., flaky, but clear. Capacity 900 cc. First washing clear. Mucous membrane entirely normal throughout bladder, a few bands noted in vertex. Both ureteral orifices normal and functioning. Trigone normal. Attempt to see verumontanum and posterior urethra unsuccessful.

Diagnosis: Normal bladder.

Neurological findings: Complete sensory anesthesia infra-orbital distribution trigeminal nerve right side. No muscular changes i.e. motor nerve involvement. Examination time of injury.

Residual urine and sexual condition: Sensory disturbances are same. Since two hours after injury patient has had trismus, due to loss of right pterygoid muscles.

Sexual findings normal.

Case XIX

A. F. K. Age twenty-four.

Date of injury: 8-9-18.

Onset of incontinence: None until last two months; since just a slight amount of leaking as noticed particularly on getting up in morning. He is conscious of same but cannot avoid it.

Lesion: 4th lumbar vertebra, involving cauda equina.

Blood urea: 7-29-19. 7.0 mgm. per 100 cc.

Creatinin: 7-29-19. 1.3 mgm. per 100 cc.

Renal function: 7-31-19. 67 per cent total excretion in two hours.

Cystoscopy: Voided specimen, 40 cc. pale and cloudy. Residual 50 cc. same. Capacity 800 cc. or more. No sensation of fullness. First washing was clear. Bladder mucous membrane shows rather marked trabeculations throughout the whole surface, except at base; most marked at summit and extending down right side to ureteral ridge. Trigone obliterated as is sphincter, making whole posterior

urethra easily visible. Prostatic ducts and verumontanum are seen and are somewhat congested. Ureteral orifices are normal.

Neurological findings: Gunshot wound at level of 4th and 5th lumbar vertebra. Lesion of cauda equina, involving 2d, 3d, 4th and 5th sacral roots, right; and 3d, 4th and parts of 2d and 5th sacral roots, left. There is paralysis of peroneal group of muscles of right leg, with more or less interference with power of other sciatic muscles; on the left side lesion is less extensive and less marked, with slight impairment of thigh, leg, and foot movements.

There is sensory loss on right side over buttocks, scrotum, back of thigh, outer surface of leg and foot and outer half of sole of foot. On left side there is impairment in the same area but loss is not so complete; and changes are very slight in the distribution of the 1st and 2d sacral areas.

There has been distinct improvement, both motor and sensory; this is also true of sphincter, which is now to some extent under voluntary control. The area of complete anesthesia is limited on the right side to distribution of 2d, 3rd, 4th and 5th sacral roots; on the left side to 3rd and 4th sacral roots chiefly.

Residual urine: Sexual powers: Patient was catheterized for four months, since which time he has been able to void with very little difficulty, although there is a persistent tendency not to incontinence. Patient states that this is lessening. His bowels are sluggish, never incontinent. He did not feel the cystoscope on examination, but has fair sense of touch and pressure in testicles. He does not have erections or emissions of semen, but says he still has the normal sexual desires.

Case XX

R. P. Age twenty-three.

Date of injury: 9-6-18.

Onset of incontinence: None at any time. Retention until May, 1919. Catheterized t.i.d. Incontinence of bowel seven to eight weeks; has had to take cathartics ever since. Since May 1919 has combined urination and defecation at intervals of about three hours.

Lesion: 5th lumbar vertebra, involving cauda equina and conus.

Blood urea: 7-23-19. 20.3 mgm. per 100 cc.

Creatinin: 7-23-19. 1.3 mgm. per 100 cc.

Renal function: 7-23-19. Two hour excretion, 57 per cent.

Cystoscopy: No voided specimen. No novocaine. No sensation urethra or bladder. No. 26 Wappler cystoscope entered bladder with

ease. Contained urine, 400 cc., clear. Capacity 900 cc. (?). First washing clear. Prostatic outline normal. Marked trabeculation of whole vault with corrugations most marked at vertex of bladder. Trigone obliterated. Both ureteral orifices normal and functioning. Sphincter obliterated, making posterior urethra visible. Verumontanum large, entirely visible, as are all openings of prostatic ducts and utricle. No evidence of active cystitis.

Neurological findings: Sensation: Hyperalgesia iliac crests over sacrum to middle of latter. From here down, involving peri-anal region and a small area on inside of thighs, scrotum, and penis, there is complete anesthesia to touch and prick. Area involved is larger on left, anteriorly and posteriorly.

Motor: No obvious paralysis lower extremities, though patient complains pain in hamstring muscles on walking. Loss voluntary control of vesical and rectal sphincters. Defecation and urination dependent on overcoming tonic contraction of internal sphincters by straining.

Reflexes: Deep are very active at patella and ankle; equal on two sides. No clonus. Superficial reflexes are active on abdomen; cremasteric present on left, absent on right.

Diagnosis: Lesion cauda equina, involving sacral nerves below 3d sacral; irritation posterior divisions 1st, and 2d sacral nerves. Slight lesion lumbar cord, level 3d lumbar segment, probably contusion. Tenderness over right sciatic throughout its course, suggestive of an irritative lesion in pelvis of spinal canal. Babinski distinct on left, suggestive on right. Lesion of 3d, 4th, 5th sacral nerves, and coccygeal nerves is probably complete interruption.

Residual findings: Patient states that sensation has improved. He shows complete anesthesia of genitalia and of bladder. No evidence of bladder irritation. Patient's habit and ability to void regularly are keeping him in good condition at present.

Sexual powers: No erection or emission of seminal fluid since injury. Sex ideas perfectly normal.

Case IV. Collateral series

P. F. C., 1st Ambulance Train, Reg., no. 26470. Age twenty-three. Previous history of incontinence negative.

No injury.

No catheterization.

Tumor spinal cord: Giant celled sarcoma 5th dorsal segment.

Operation: 4-3-19. Walter Reed General Hospital. Removal of tumor.

Blood urea: 4-26-19. 11.2 mgm. per 100 cc. plasma.

Creatinin: 4-26-19. 1.25 mgm. per 100 cc. plasma.

Cystoscopy: 4-26-19. Residual urine 335 cc. Clear. Prostatic outline congested, normal outline. Trabeculations lateral wall left side only. Right ureteral orifice slightly dilated but not immobile. Left ureteral orifice normal. Trigone raised by comparison. Bas fond present, not marked. Posterior urethra dilated. Verumontanum plainly seen with ordinary cystoscope. No evidence of cystitis.

Renal function: 17 per cent + 17 per cent. (25 cc. residual urine after 2d hour.)

Trophic ulcer: Right heel, small.

Blood count: 2-26-19. W.B.C. 16,550.

Rectum: Obstipated always.

Hemoglobin: 85 per cent.

Sexual powers: Normal.

Spinal fluid: Wassermann negative. Cell count 2.

Hyperidrosis: No. Not complained of at any time.

TABLE 1

The Monthly Relations Between Retention of Urea Nitrogen and Excretion of Phenolsulphonphthalein.

(1)	(2)		(3)	(4)		(5)	(6)	
<i>Feb.</i> V. 23.3 mgm. 30+15	V. 94.0 mgm. 25+10		V. 80 mgm. 15+20	V. 56 mgm. 25+15		V. 15.4 mgm. 30+20	103.0 20+45	
<i>March</i> 16.8 45+30	19.8 20+25		15.8 55+25	19.0 30+15		26.6	Dead	
<i>April</i> 10.2 40+16	10.2 32+20		8.4 42+19	8.2 35+15		30.0 5+15 Sick		
<i>May</i> 5.6 30+20				15.8 42+18				

(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
<i>Feb.</i> 48.0 20+30		105.0 Lost	112.0 0	13.8 60+12			93.0 2+2			
<i>March</i> 26.0 50+25	65.0 50+35	21.0 22+15	28.4 2+2	67.2 0	24.9 50+20	28.9 20+15	21.4 41+18	11.98 20+20		
<i>April</i> 18.2 42+17	12.8 50+22	16.0 20+22	32.6 6+9	Dead	14.0 42+19	24.2 13+6	8.4 40+16	22.1 38+15	9.32 42+16	14.2 37+17
<i>May</i> 11.2 62+19	11.18 48+12	10.2 58+28	31.6 2+7 Very sick 25.0 9+12 Improved							

Note: No. 10 was slowly improving when the fifth reading was done. Note the rise in phenolsulphonphthalein as urea nitrogen decreases. This was an automatic bladder, with profound disturbance.

Note the persistent retention of nitrogen in this case, even after careful daily removal of residual. This is probably due to renal infection, and would be a better indication of the danger of operation on the lower tract than the creatinin which remained at 2 mgm. per 100 cc. plasma.

The above table simply shows in epitome the monthly relations between retention of urea nitrogen and excretion of phenolsulphonphthalein. In each monthly block the upper figure represents milligrams of urea nitrogen per 100 cc. of blood plasma, the lower figures showing the output of phenolsulphonphthalein in two periods of seventy and sixty minutes, respectively.

TABLE 2
Statistical Results in Selected Cases

CASE	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)				(13)				(14)				(15)				(16)				(17)				(18)				(19)				(20)																							
												TOTAL				URINE				BLOOD				Gms. per 24 hours				Mgm. per 100 cc.				Urea nitrogen				Creatinin				Uric acid				NaCl.				Creatinin				Uric acid				First day				Second day							
												FUNCTIONAL PHENOL-SULPHON-PHTHALEIN FIRST HOUR				FUNCTIONAL PHENOL-SULPHON-PHTHALEIN SECOND HOUR				Urea nitrogen				Non-protein nitrogen				Creatinin				Uric acid				Urea nitrogen				Creatinin				Uric acid				NaCl.				Creatinin				Uric acid				First day				Second day			
												BODY WEIGHT				pounds				FUNCTIONAL PHENOL-SULPHON-PHTHALEIN FIRST HOUR				FUNCTIONAL PHENOL-SULPHON-PHTHALEIN SECOND HOUR				TOTAL				Urea nitrogen				Non-protein nitrogen				Creatinin				Uric acid				Urea nitrogen				Creatinin				Uric acid				NaCl.				Creatinin			
No. 10 Reg. No. 25062	23	2d Lt.	4-29-19	100	70	Clear	1600	114	2% 0	7%	29 9	113.0 31.6	66.6 2.0	3.4	18.0	395	912	727	1918	1034	1289																																														
No. 4 Reg. No. 22700	25	Pvt.	4-30-19	45	75	Reddish alkaline	1150	110	25 42%	15 18%	40 60	56.0 15.8	46.0 1.5	0.2	6.1	432	340	400	1014	1289																																															
No. 2 Reg. No. 24931	23	Pvt.	5- 1-19	70	165	Reddish alkaline	830	133	25 30%	10 20%	35 50	94.0 5.6	50.0 1.5	0.0	5.0	592	470	1000	1357	1347																																															
No. 9 Reg. No. 25601	30	2d Lt.	5- 2-19	180	85	Reddish alkaline	1750	114	22 52%	15 28%	37 80	105.0 10.2	44.0 1.4	1.9	10.3	526	1130		1766	1838																																															
No. 8 Reg. No. 25918	23	Pvt.	5- 3-19	175	100	Cloudy	2600	131½	50 48%	35 12%	85 60	65.0 1.18	46.0 1.3	1.4	11.0	561	577	260	1142	1504																																															
No. 7 Reg. No. 22710	27	Pvt.	5- 4-19	275	115	Reddish alkaline	2000	122	62%	19%	81	11.2	45.0	1.1	2.1	11.0	370	525	320	1158	1698																																														

Controls

1	23	Pvt.	4-28-19	350 voided	50 voided	Clear	1200	140	40%	14%	54	12.1	36.6	1.0	2.0	11.4	666	2172	852	1500	1500
2	25	P. F. C.	4-28-19	325 voided	70 voided	Clear	1300	132	44%	11%	55	13.0	40.0	1.15	2.2	11.8	617	912	850	1500	1500

At the time these cases were done, the first three were in distinctly bad condition, the last three were distinctly improving. The results, as tabulated, were rather surprising, but one week after the data were obtained cases IV and II changed markedly in improvement, and are steadily progressing upward. Case X, with persistent high urea did not improve, as we were able to prognose from these findings.

In columns 9, 10, 11, 12, the upper figures show values obtained when first seen, the lower figures show values at end of third month of observation. The phenolsulphophthaleins in this series were all intramuscular, either deltoid or gluteal.

Where the blood urea is low and the urinary urea also low, the cases are showing marked clinical improvement, and the greater the drop below normal the more marked is there a picture of tissue resorption. This is especially true of cases II and IX. Cases VII and VIII have been upbuilding so long they are no longer reabsorbing into the tissues.

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ROUTINE EXAMINATION OF THE BLADDER IN SECONDARY SYPHILIS

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Secondary syphilis manifests itself most strikingly upon the skin and mucous membranes. At the time of the appearance of the first eruption clinical manifestations of visceral origin are unusual. A reaction is occurring on the part of the tissues; however, only after varying intervals, frequently years after infection, does it manifest itself in the form of an aortitis, a cirrhosis, a tabes, a general paresis. Theobald Smith characterizes the *treponema pallidum* as an organism which may dispense largely with both offensive and defensive processes, and which exerts a metabolic activity approximating so closely to that of the host that the latter reacts but slightly and then only after a long period of stimulation.

There is a type of secondary lesion, however, which might be expected to occur frequently in certain viscera, namely, lesions involving the lining mucosa and corresponding to syphilides appearing on the more accessible mucous membranes. Of these viscera the bladder lends itself readily to examination.

The literature on syphilis of the bladder deals chiefly with tertiary lesions, and case-reports of gummata are fairly numerous. Secondary lesions have been observed in relatively few cases. Tarnowsky (1) in 1862 reported the case of a child, infected extragenitally, presenting lesions at the mouth and anus, also an ulcerative syphilide, and with apparently considerable dysuria. Autopsy showed ulcerations of the bladder and urethra which were considered syphilitic.

Fenwick (2) in 1879 examined the bladder of a male with a genital chancre, who died from stab-wounds, and found numerous papules on the vesical mucous membrane.

Newmann (3) briefly mentions a case in which numerous small papules were disseminated over the bladder wall and classifies the lesions as small gummata. Asch in discussing the case concludes the picture is really one of secondary syphilis.

In 1902 Pereschiwkin (4) published three cases of vesical lesions occurring during florid secondary syphilis. Each of the patients presented urinary disturbances in the form of urgency and dysuria, and showed on cystoscopy several small ulcerations with infiltrated edges. Both symptoms and lesions disappeared rapidly as a result of mercurial treatment.

Mucharinsky's (5) case is questionable, as there was cystitis and retention, and treatment consisted of local applications as well as the administration of anti-syphilitics.

Frank (6) at the Urological Congress of Berlin in 1909 demonstrated plates of two cases of secondary syphilis of the bladder, showing the rapid improvement following mercurial treatment. In all he had encountered five such cases.

Asch (7) in 1911 reported the case of a woman, infected fifteen months previously, who had suffered from frequency and dysuria for nine months. Cystoscopy revealed an edematous and hyperemic mucosa with about six superficial ulcerations. At the end of six weeks of anti-syphilitics the mucosa was normal.

In 1913 Levy-Bing and Durouex (8) performed routine cystoscopies on a series of syphilitics with secondary manifestations. One case with a roseola and lesions on the soft palate and uvula, presenting no urinary symptoms, disclosed between the median line and the left ureteral orifice a zone of hyperemia, sharply differentiated from the normal mucosa and traversed by numerous distended vessels. In this area were scattered ten small round or oval ulcers with edges of infiltration. Mercurial treatment produced complete disappearance of these lesions. In several other cases there occurred hyperemia of the mucosa; one of these showed a well defined area of hyperemia in which were scattered fourteen deeper red lentil sized spots, which the authors considered to correspond to a macular syphilide.

Twenty-four male patients with active secondary syphilis were selected for this investigation. Nine cases presented macular

syphilides, twelve a papular eruption and in three the eruption was pustular. In eighteen there were lesions on the mucous membranes of the mouth and pharynx or moist lesions about the anus or on the scrotum. The cases were carefully selected; those having urological conditions, which might explain urinary symptoms, were excluded at once. All were given a routine urological examination before cystoscopy. The patients were re-cystoscoped if the changes in the bladder made further investigation advisable.

RESULTS

In no case were urinary symptoms present and examination of the urine was negative, except for a few shreds in the first glass in a few cases of chronic urethritis.

No striking bladder changes were discovered. In ten cases slight vascular changes were noted in the region of the trigone in the form of a delicate ramifying network and on the bladder wall itself as an increase in the calibre of the vessels. The vascular changes were not considered significant.

None of these cases presented either papular or ulcerative lesions. In one with a macular syphilide of the skin, evidences of a macular lesion were found with changes almost identical to one of the cases described by Levy-Bing and Duroeux, except that the lesions were confined to the trigone instead of to the bladder wall. The trigone was flat and remarkable for the congestion present, without any edema. The blood vessels were conspicuous as longitudinal striae. In this area were scattered about six pin-head to pea-sized spots of a deeper red color. The erythema ended abruptly at the ligamentum uretericum. The rest of the bladder was normal. The limitation of these redder spots to the trigone makes it unlikely that they were syphilitic macules. It is a well known fact that changes in the trigone without involvement of the vesical mucosa is often secondary to a chronic posterior urethritis and prostatitis. In this case the patient's prostatic condition suggested a moderate degree of chronic infection. His urine was microscopically and chemically negative. The patient left Baltimore after one injection of arsphenamin, thus preventing further study of the bladder.

CONCLUSIONS

Bladder changes in secondary syphilis are insignificant. Vascular changes have been observed, both of the trigone and of the vesical mucous membrane, but not sufficiently characteristic to make them luetic manifestations. In one case lesions suggesting a macular rash were seen limited to the trigone.

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ON THE EFFECT OF PROSTATE FEEDING ON THE DEVELOPMENT OF TADPOLES¹

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The importance of endocrine glands has been more and more recognized in the last two years and numerous papers and books have been written on the subject. Among those glands concerning the function of which there is very little known in this respect is the prostate. While the physiological properties of the *external* secretion of that gland are generally recognized as essential for the life of spermatozoa, the question whether the prostate also furnishes an *internal* secretion is still in dispute. The chief evidence in favor of an internal secretion of this gland is the work of Serralach and Pares. These authors found that prostatectomy in dogs was followed by a gradual atrophy and degeneration of the function of the testes and that these defects could be prevented by injections of glycerine extracts of prostate. In connection with a physiological and pharmacological study of prostatic extracts which the author has been conducting for some time, he observed the effect of feeding prostate on the growth and development of tadpoles. In the present paper, it is proposed to give a preliminary account of these observations which turned out to be of unusual interest.

In the experiments performed, frogs' larvae were placed in convenient receptacles and some of them were fed desiccated prostate of the ram, bull, and other animals, while others were kept as controls and given other glandular extracts or tissues. In every experiment tadpoles of exactly the same age and size were selected. These were kept in the same kind of vessel in equal parts of

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water and under exactly the same conditions of light and temperature. The following species of frogs' larvae were studied: *Rana sylvatica*, *Rana palustris*, and *Rana catesbiana*.

The effect of feeding prostate gland to the larvae was very striking and interesting. It was found that the metabolism of the tadpoles was stimulated by the prostate feeding and that their metamorphosis was hastened. In other words, the tadpoles developed legs earlier than normally and were soon transformed into frogs. At the same time the size of the tadpoles was not



FIG. 1. *RANA SYLVATICA*

After two weeks' feeding ram's prostate. A, normal; B, prostate.

FIG. 2. *RANA PALUSTRIS*

Two weeks' feeding of desiccated prostate (ram). Note metamorphosis and size. B, prostate; A, normal.

FIG. 3. *RANA PALUSTRIS*

Bull's prostate fed May 9-26. Note metamorphosis and increase in size. A, normal; B, prostate.

diminished and indeed in many cases the tadpoles also increased in size. This effect was produced by feeding the desiccated prostate of the ram (Armour) and also the desiccated prostate of bulls and in a few experiments followed the feeding of human prostate.

The above peculiar effect of prostate feeding on the development of tadpoles has never been observed or reported before. In connection with these observations, we must of course recall the classical experiments of Gudernatsch who found that the

feeding of thyroid hastens the metamorphosis of frogs' larvae. Unlike the case of the thyroid, however, the prostate does not produce a shrinkage or dwarfing in the size of the tadpoles, but on the contrary usually stimulates their growth; while the thyroid, as is well known, from the experiments of Gudernatsch, Rogoff and others, produces a very marked atrophy or shrinkage of the organisms.

Control experiments made with all kinds of desiccated glands—ovary, corpus luteum, parotid, liver, testes, etc.—failed to produce the remarkably stimulating effect on metamorphosis shown by the thyroid and the prostate.

Following the experiments on frogs' larvae, the author made further observations on the larvae of the toad, *Bufo lentiginosus*, and here again it was found that the toad larvae which were fed on prostate gland metamorphosed more rapidly than the other tadpoles which were of the same age and size at the beginning of the experiment. The author then was fortunate in obtaining recently laid eggs of the salamander, *Amblystoma punctata*. As soon as the larvae were hatched, observations were begun on the effect of prostate feeding on their growth and development. Ordinarily, these salamander larvae grow and metamorphose very slowly (several months). It was surprising, therefore, to find that feeding of the prostate gland induced changes in the organisms in as early as two weeks time. It was noted that those larvae which were administered the prostatic extracts increased in size and began to develop their hind extremities at a very early date. In other words, the effect on salamander larvae was the same as in case of the frog and toad.

The above observations are still in progress, but the author has collected a sufficient number of experiments to be able to assert that the peculiar effect of the prostate gland when fed to tadpoles is not an accidental one but is a distinct and definite physiological phenomenon. Such a phenomenon speaks strongly in favor of an internal secretion of the prostate gland. The author is conducting further observations concerning the effect of prostate feeding on rats, kittens, and other animals. The more complete data will appear in due time in the Journal of Urology.

TOXICITY OF PYELOGRAPHIC MEDIUMS

REPORT OF A DEATH FOLLOWING THE USE OF THORIUM NITRATE

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There is no longer any question as to the value of pyelography. Whenever renal catheterization is necessary for diagnostic purposes the procedure is almost routine. Urologists have sought an opaque medium which would not be injurious, and all experimental work in the past has been done with the view of determining the effect of pyelographic mediums on the kidney tissue. It has been shown definitely that colloidal silver solutions are injurious to the kidney tissue and that they get into the circulation. I have recently shown that all pyelographic mediums and various dyes are rapidly absorbed from the kidney pelvis. The striking clinical results that are often obtained in cases of pyelonephritis by pelvic lavage with silver nitrate solutions have been explained as due to the action of the silver solution, not only by its local effect on the kidney pelvis but also by its permeation of the kidney tubules (Braasch). In view of the work we have done in demonstrating that substances are absorbed from the tubules of the medullary portion, it seems plausible that such an explanation of the action of silver nitrate is correct. A recent death following pyelography for which a solution of thorium nitrate was used led us to make a study of the toxicity of the different pyelographic mediums.

Case 64235. A woman, aged 55, was examined at the Mayo Clinic February 27, 1919, and died following a ureteral catheterization in which thorium nitrate was used as the pyelographic medium. The patient first came to the clinic in February, 1912, at which time she complained of pain with epigastric distress, rather typical of gall-bladder

disease. A cholecystostomy was performed and a chronic catarrhal cholecystitis (strawberry gall-bladder) with a large number of stones was found. Recovery was uneventful and the patient was in good health until three months before her last examination; she then began to have attacks of epigastric distress coming on at night every two weeks; a dull severe ache with a sensation of fullness at the right costal border which would last two or three hours. She complained of some indefinite urinary symptoms. The examination of the urine showed it to be practically normal. The hemoglobin was 77 per cent; x-ray examination of kidneys, ureters, and bladder was negative.

The patient was given a cystoscopic examination in order to identify the source of the abdominal pain. A slight irritability of the bladder with a few areas of chronic inflammation, particularly at the right and left base of the bladder, was noted. Both ureters were of normal length and the secretion was clear. A specimen showed a moderate number of red blood cells. A differential functional test showed 17 per cent on the right and 12 per cent on the left with a return flow from the bladder of 2 per cent. Because of the right-sided pain a pyelogram was made. Thorium nitrate, prepared by a well known pharmaceutical company, was the opaque medium used and was carefully injected. The patient did not complain of pain, she was somewhat weak and faint for a short time after getting off the table, but was able to go to her hotel. At the end of six hours she was suddenly seized with nausea, vertigo, and weakness. The symptoms became rapidly worse, with pronounced vomiting, and prostration, and she died at 7 p.m., nine hours after the pyelogram was made.

The clinical diagnosis was negative so far as a pathologic condition in the kidney was concerned. The nature of her death suggested acute toxemia, evidently the result of pyelography.

At necropsy marked general arterial sclerosis, moderate fibrosis, fatty myocarditis, arteriosclerotic atrophy of the kidney, slight traumatic hemorrhage in the pelvis of the right kidney, slight catheterization, bruising of the urethra and ureteral mouths, marked edema of both lungs, small hypernephroma of the right adrenal gland, the size of a bean, right apical fibrous adhesive pleuritis, old atrophic cholecystostomy scar of the abdomen, moderate arteriosclerotic deformity of the gall-bladder, fibrous adhesions between the gall-bladder, parietal peritoneum, hepatic flexure of the colon, first portion of the duodenum, and the under surface of the liver, marked parenchymatous fatty changes in the liver, slight hyperplasia of the spleen, and petechial

hemorrhages in the mucous lining of the greater antrum of the stomach were found. Microscopic examination of the kidney showed some cloudiness of the tubular epithelium, with areas of acute congestion.

The stock of thorium nitrate solution on hand at the time was at once sent to the manufacturer, but unfortunately none was saved to be tested physiologically in our own laboratories. Several specimens of thorium nitrate solution of different ages were tested, however, and these showed varying toxicity.

PHYSIOLOGIC TESTS OF THE TOXICITY OF THE MEDIUMS

Dogs were anesthetized and kept under light constant ether tension by the Connell apparatus. The carotid artery was arranged to record carotid blood pressure (mercury manometer). The femoral vein was exposed so that injections could be made easily either by syringe or burette. A 25 per cent solution of sodium bromid, a 25 per cent solution of potassium iodid, a 25 per cent solution of sodium iodid, and a 15 per cent solution of thorium nitrate were tested. The intravenous injection of sodium bromid in four different dogs produced practically no effect, even when 55 cc. were given. Usually there was a slight increase in blood pressure, possibly due to an increase in the fluid volume. The injection of 2 or 3 cc. of a 25 per cent solution potassium iodid caused the blood pressure to drop to zero, and almost instant death. When 50 cc. of a 25 per cent solution of sodium iodid were used in two experiments, a very slight reaction followed from which the animal soon recovered. The toxicity of the 15 per cent solutions of thorium nitrate seemed to vary with the different ages of the solutions. Twenty-two cubic centimeters from Bottle A caused the death of the animal. Ten cubic centimeters from Bottle B caused a decided reaction noted in the blood pressure curve. One hundred cubic centimeters from Bottle C produced no apparent reaction. Fifty cubic centimeters from Bottle D caused the death of the animal. Forty cubic centimeters from Bottle E caused death, as did also 25 cc. from Bottle E, when the solution was given to a slightly smaller animal. The contents of Bottle A was approximately one year old, of Bottle B approximately two months; Bottles C, D, and E had just been received from the manufacturers.

Potassium iodid should be used with great care as a pyelographic medium because of its toxicity and because of the fact that it is readily absorbed from the kidney pelvis. Death following the use of potassium iodid is very evidently due to the potassium radicle, since sodium iodid produces very little effect.

At least one of the toxic effects of thorium nitrate is on the heart muscle, as may be shown by the fact that cardiac failure follows the administration of thorium nitrate even after section of the vagi and the administration of such drugs as nicotin and atropin. Thorium nitrate seems to vary in toxicity according to the age of the solution, possibly because of the conditions under which it is kept.

Unfortunately, sodium or potassium iodid, when used in the renal pelvis and bladder in man often causes considerable local irritation in a solution of 20 to 25 per cent as originally recommended.

Sodium bromid is non-toxic, cheap, easily prepared, readily accessible, non-irritating, and would seem to be the best medium yet brought forward. We advise a 20 per cent solution for pyelography; a 10 or 15 per cent solution is sufficient for cystography. The drug should be chemically pure, and the solution should be sterilized by boiling before it is used.

PROTOCOLS

Experiment 300, Dog D124, April 22, 1919. A dog weighing 5 kg. was prepared in the usual manner. In one and one-fourth minutes 1 cc. of a 25 per cent solution of sodium bromid was injected into the right femoral vein; the pulse rate remained practically unaffected but the blood pressure was raised about 3 mm.

After allowing forty-five minutes for the dog to recover, 1 cc. of a 25 per cent solution of potassium iodid was injected in one and one-fourth minutes. A decided reaction, probably toxic, followed.

The dog was allowed forty-five minutes in which to recover and 1 cc. of a 15 per cent solution of thorium nitrate was injected which caused a slight irregular pulse curve. The solution, approximately one year old, came from Bottle A.

After eighteen minutes, 5 cc. of thorium nitrate were injected in two and one-half minutes; this caused a rise in blood pressure of about

30 mm. which gradually decreased for three minutes, and then the blood pressure seemed to remain normal. The solution came from Bottle A.

Again after eighteen minutes 5 cc. of a 25 per cent solution of sodium bromid were injected which caused a very slight rise of blood pressure,

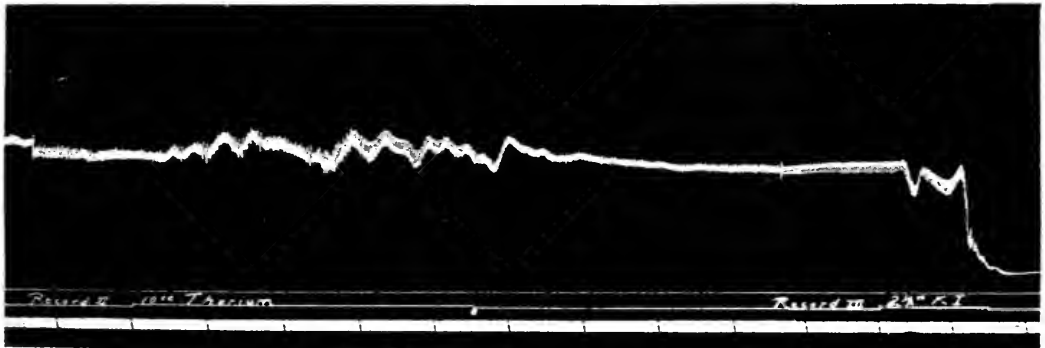


FIG. 1

Record 1, the injection of 10 cc. of 25 per cent solution sodium bromid.

Record 2, the injection of 10 cc. of 15 per cent solution thorium nitrate.

Record 3, the injection of 2.5 cc. of 25 per cent solution potassium iodid causing death (experiment 306, dog D106).

and after another eighteen minutes 2 cc. of a 25 per cent solution of potassium iodid were injected into the femoral vein. This caused a rapid fall in blood pressure and the death of the animal.

Experiment 306, Dog D106, April 22, 1919. A dog weighing 4.5 kg. was injected with 10 cc. of a 25 per cent solution of potassium iodid

into the right femoral vein at the rate of 2 cc. a minute. The blood pressure rose 6 mm. and the pulse curve was increased slightly in amplitude. After the completion of the injection the blood pressure returned to normal.

The animal was allowed forty-five minutes in which to recover when 10 cc. of thorium were injected at the rate of 2 cc. a minute. This gave a decided toxic curve and a slight rise in blood pressure, after which the curve returned to normal. The solution, approximately two months old, was taken from Bottle B.

After fifteen minutes the injection of 2.5 cc. of a 25 per cent solution of potassium iodid at the rate of 2 cc. a minute caused the immediate death of the animal (Figs. 1 and 2).

Experiment 311, Dog D131, April 23, 1919. A dog weighing 4.9 kg. was injected with a 15 per cent solution of thorium nitrate allowed

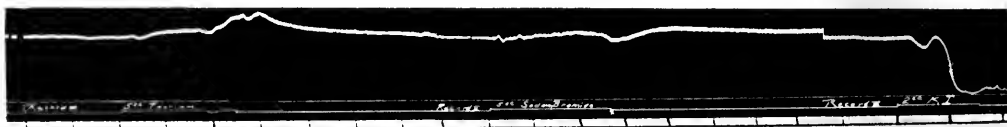


FIG. 2

Record 4, the injection of 5 cc. of 15 per cent solution thorium nitrate in the vein.

Record 5, the injection of 5 cc. of 25 per cent solution sodium bromid in the vein.

Record 6, the injection of 2 cc. of 25 per cent solution potassium iodid in the vein (experiment 306, dog D106).

to flow by gravity from a burette into the right femoral vein. For the first three minutes the rate was 1 cc. a minute; 5 cc. had entered in four minutes, 8 cc. in six minutes, 10 cc. in eight minutes, 16 cc. in nine minutes, 20 cc. in ten minutes, and 22 cc. in eleven minutes, at which time the animal died. It is probable that the animal would have died if a smaller quantity had been used. The solution, approximately one year old, came from Bottle A (Fig. 3).

Experiment 312, Dog D132, April 23, 1919. A dog weighing 4.7 kg. was injected with a 25 per cent solution of sodium bromid allowed to flow slowly from a burette into the right femoral vein at the rates noted in the preceding experiment. Thirty cubic centimeters were injected in thirteen minutes without causing any marked reaction. The blood pressure rose slightly, and the pulse seemed to increase in volume.

The animal was allowed to remain on the table thirty minutes, and another record was taken (Fig. 4).

Experiment 314, Dog C268, April 24, 1919. A dog weighing 12 kg. was injected with a 15 per cent solution of thorium nitrate, allowed to flow gradually from a burette into the left femoral vein. Six cubic centimeters had entered in five minutes, 10 cc. in eight minutes, 30 cc. in thirteen minutes, 50 cc. in eighteen and one-half minutes. Following this the animal was given one hour in which to recover when 50 cc. more were allowed to flow into the vein in thirteen minutes. This injection did not seem to have any toxic effect on the dog. The solution, approximately one month old, came from Bottle C which had recently been received from the manufacturer.

Experiment 316, Dog D135, April 28, 1919. A dog weighing 7.2 kg. was injected with a 25 per cent solution of sodium bromid allowed to

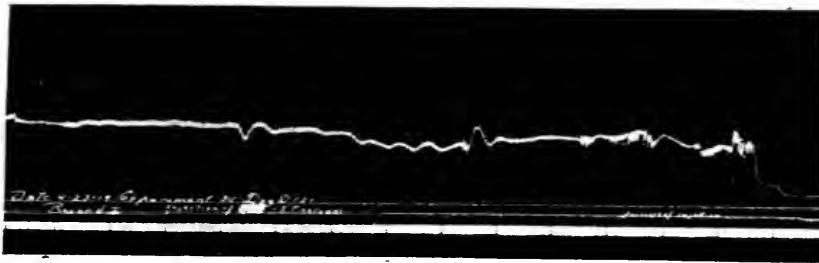


FIG. 3. Death of a dog following the injection of 22 cc. of a 15 per cent solution of thorium nitrate (experiment 311, dog D131).

run by gravity from a burette into the left femoral vein at the rate of 3 cc. in three minutes, 6 cc. in eight minutes, and 55 cc. in eleven minutes. This produced no ill effect. There was a slight rise in blood pressure which gradually returned to normal after the injection had been discontinued. The animal was killed by injecting 2.5 cc. of 15 per cent colloidal silver solution directly into the vein.

Experiment 317, Dog D136, April 28, 1919. A dog weighing 10.4 kg. was injected with thorium nitrate allowed to run by gravity from a burette into the left femoral vein. In the first minute 6 cc. were injected, causing a rapid fall in blood pressure. The animal was allowed one minute in which to recover. At the end of three minutes 9 cc. had been injected, in four minutes 12 cc., in five minutes 14 cc., in six minutes 17 cc., in seven minutes 21 cc., in eight minutes 32 cc., in nine minutes 37 cc., in ten minutes 41 cc., in eleven minutes 44 cc., in twelve



FIG. 4. The injection of 30 cc. of 25 per cent solution of sodium bromid (experiment 312, dog D132).



FIG. 5. Death of a dog following the injection of 50 cc. of thorium nitrate solution (experiment 317, dog D136).

minutes 47 cc., in thirteen minutes 50 cc. The solution was then injected at the approximate rate of 4 cc. a minute. At the end of eight minutes the blood pressure gradually began to drop, and continued to fall until 50 cc. had been injected when the animal died. The solution was taken from a bottle (Bottle D) which had been received from the manufacturer about one week before. The bottle had never been opened until it was used in this experiment (Fig. 5).

Experiment 319, Dog D138, April 29, 1919. A dog weighing 9 kg. was injected with thorium nitrate solution allowed to flow from a burette into the left femoral vein. In one minute 4 cc. were injected, 10 cc. in two minutes, 15 cc. in three minutes, 20 cc. in four minutes, 25 cc. in five minutes, 30 cc. in six minutes, 34 cc. in seven minutes, 38 cc. in eight minutes, 40 cc. in eight and one-half minutes at which



FIG. 6. Death following the injection of 40 cc. of thorium nitrate solution (experiment 319, dog D138).

time the animal died. The blood pressure had risen gradually until 30 cc. had been given, and then it began to sink in a more rapid curve than that in which it had risen until death ensued three minutes later. The solution, which had not been used until this experiment, was taken from Bottle E (Fig. 6).

Experiment 321, Dog D140, April 30, 1919. A dog weighing 5.2 kg. was injected from a burette arranged to allow a 25 per cent solution of sodium iodid to flow into the right femoral vein. In one minute 3 cc. were injected, in two minutes 6 cc., in three minutes 9 cc., in four minutes 13 cc., in five minutes 17 cc., in six minutes 20 cc., in eight minutes 25 cc., in nine minutes 30 cc. The curve was somewhat irregular at this time due to very light anesthesia. In ten minutes 33 cc. were injected, in eleven minutes 40 cc. The animal struggled somewhat, due to light anesthesia. In thirteen minutes 44 cc. were

injected, in fourteen minutes 50 cc. There was apparently very little toxic effect. The animal was given 2 cc. potassium iodid which caused instant death, apparently from heart failure.

Experiment 327, Dog D141, May 1, 1919. A dog weighing 5.4 kg. was injected with a 25 per cent solution of sodium iodid allowed to flow from a burette into the right femoral vein. In one minute 1.5 cc. were injected, in two minutes 4.5 cc., in three minutes 8 cc., in four minutes 11 cc., in five minutes 16 cc. At this time there was a slight fall in blood pressure because of the too rapid injection. In six minutes 21 cc. were injected, in seven minutes 24 cc., in eight minutes 31 cc. The blood pressure fell again because of too rapid injection. In nine minutes 35 cc. were injected, in ten minutes 43 cc., in eleven minutes 50 cc. The record was stopped; after fifteen minutes it was run for a short interval showing that the blood pressure had risen about 20 mm.

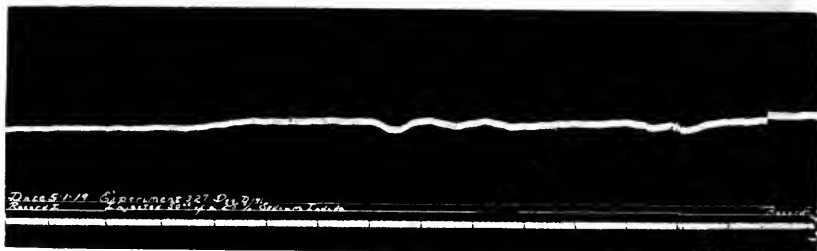


FIG. 7. The injection of 50 cc. of a 25 per cent solution of sodium iodid (experiment 327, dog D141).

above the original. From this experiment it would seem that sodium iodid is non-toxic but when given rapidly intravenously causes a slight reaction (Fig. 7).

Experiment 335, Dog D144, May 6, 1919. A dog weighing 5.8 kg. with blood pressure of 150 mm. was injected with 15 cc. of a 15 per cent thorium nitrate solution taken from Bottle E and allowed to flow from a burette into the femoral vein at the rate of 3 cc. a minute. The blood pressure gradually rose until it reached 200 mm. at the end of five minutes when it began to fall slightly; the injection was, therefore, discontinued. The pulse became very slow and full, increasing to a large pulse pressure after the injection was stopped. The blood pressure in the meantime rose to 230 mm. Two minutes after the injection was stopped the blood pressure gradually began to fall and at the end of forty-five minutes it had dropped to 110 mm.; at this time Record 2



FIG. 8

Record 1, the injection of 15 cc. of a 15 per cent solution of thorium nitrate. The injection was stopped at "A" and animal allowed to recover. The rate of injection was 3 cc. per minute.

Record 2, the injection of 10 cc. of a 15 per cent solution of thorium nitrate in one and one-fourth minutes causing rapid fall in blood pressure and finally death of the dog (experiment 335, dog D144).

was taken. Ten cubic centimeters of a 15 per cent solution thorium nitrate were then injected in one and one-fourth minutes. This caused a rapid rise in blood pressure up to 165 mm. in one minute. The blood pressure began to fall, the heart became very slow, but recovered and the record was continued for twenty minutes and showed the gradual fall of the blood pressure, while the pulse pressure was large and the pulse very slow and full. As it was evident at the end of twenty minutes that the animal would die, the vagi were sectioned. This had no effect on the pulse or blood pressure, proving that the toxic effect was not on the central nervous system (Record 3, Signal C). Nicotin injected intravenously produced no effect; this showed that the effect of the drug was not on the nerve ganglion. Atropin was injected and produced no effect, showing that the action was not on the nerve endings. The animal would probably have been killed at the first injection if more than 15 cc. had been given. The action of the drug is directly on the heart, particularly when a large dose is given rapidly (Fig. 8).

Physiologic tests of the toxicity of pyelographic mediums

EXPERIMENT	25 PER CENT SODIUM BROMID		BOTTLE	15 PER CENT THORIUM NITRATE		25 PER CENT POTASSIUM IODID		25 PER CENT SODIUM IODID	
	Amount	Reaction		Amount	Reaction	Amount	Reaction	Amount	Reaction
	cc.			cc.		cc.		cc.	
300	1	None	A	1	None	1.0	Toxic		
300	5	None	A	5	Slight	2.0	Death		
306	10	None	B	10	Toxic	2.5	Death		
311			A	22	Death				
312	30	None							
314			C	100	None				
316	55	None							
317			D	50	Death				
319			E	40	Death				
321								50	None
327								50	Very slight
335			E	25	Death				

REFERENCE

- (1) CAMERON, D. F.: Aqueous solutions of potassium and sodium iodids as opaque mediums in roentgenography. Preliminary report. Jour. Am. Med. Assn., 1918, lxx, 754-755.

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MASSIVE DEGENERATION IN TUBERCULOSIS OF THE KIDNEY AND ITS RÔLE IN THE CLINICAL CURE¹

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The question of the possibility of spontaneous healing, or a non-surgical cure, of renal tuberculosis has been practically answered, for the clinician, in the negative. Ever since Albarán, fifteen years ago, with the full weight of his authority and the results of his operative statistics, first laid down the principle that cure depended upon an early operation, it has been accepted that clinical cure depended upon surgery and surgery alone. However we must draw a distinction between clinical cure and anatomic healing, and in doing so deal not too grossly, nor too sweepingly, in pronouncing the fact that because clinical cure in the vast majority of cases depends upon surgical removal that actual healing never occurs. That there may be cases of minor intensity, virulence, and involvement, that pass to a healed condition without ever being clinically manifest is one possibility; and at the other extreme are cases passing on to complete destruction, ending in isolation and a total sterilization of the infectious process. That these latter cases may have the infection limited to this one organ is compatible with our knowledge of tuberculosis as it affects other organs of the body, and though rare in regard to the kidney, is nevertheless demonstrable.

Is it not contrary to our knowledge of tuberculosis as it affects other organs (bone, gland, or lung), to hold that the kidney once the seat of tuberculous infection is doomed to complete destruction? Or that once invaded it is beyond the power of nature to perform here what it does elsewhere and what we know to be

¹ Read before the Academy of Surgery, Philadelphia, December 3, 1917.

nature's tendency in every other such condition, that is, to accomplish a segregation of the infected tissue and in time to complete an anatomic healing? That such is a possibility in renal tuberculosis has now been well established by a few carefully studied cases of unquestioned authorities, and in recording the case herein reported I do so, feeling that it is urgent that all such material be placed on record, so that our view may be broadened and deductions made possible at a future date, from sufficiently overwhelming circumstantial evidence.

In the beginning let me state that I know that such an outcome as anatomic healing of a completely destroyed tuberculous kidney is of the rarest circumstance, and most emphatically is not to be assumed or favored as a prognostic chance; in fact it is the rarity of the condition that makes it interesting.

Some there are who demand in an academic way that before a kidney can be pronounced healed of a tuberculous infection it should be restored to its former healthy condition. Better let us realize in the beginning that kidney tuberculosis is essentially a destructive lesion, showing in the vast majority of cases little or no tendency toward repair, and likewise to appreciate that such destruction may vary in its form, location, and extent, from a small focus in one pole to a complete involvement of the entire organ. Therefore it is not to be expected either from a surgical, a pathologic, or a physiologic point of view, that healing of such an infectious process of necessity implies a restitution of normal contour and function. Similar and various other lesions occurring in other parts of the body are brought to a standstill by some method, or feat of nature, and are considered healed and cured without a return to normal outline and function. So that I cannot help but voice the sentiment that we are attempting to strive at an ideal unattainable, when we demand of renal tuberculosis—as some do—what we do not stipulate when pronouncing a similar conclusion in regard to other deforming lesions.

The clinical surgeon and the pathologist are not of one opinion when it comes to agreeing as to the origin of a tuberculous infection of the kidney, nor as to its source, its mode of trans-

mission, its localization, or its progressive stages, and it has been impossible to sufficiently correlate the various opinions from such men as Walker, Tuffier, Albarran, Pousson, Desnos and Minet, Legueu, Israel, and others so as to give here a lucid expression or a uniform classification of the lesions of chronic renal tuberculosis. An enormous literature has accumulated on the subject, for it is reported that in the last ten years alone over one thousand five hundred articles have been published. There is, however, one man whose writings on the subject of renal tuberculosis have been fruitful of more progress than that of any one other investigator, and whose name has been constantly associated with the subject for more than twenty-five years, and I feel that Noel Hallé has so simplified the pathology and has so accurately outlined the various stages in the progress of the disease, that I will adopt and expound his recently published views only, as being expressive of the best thought of the day and in order to show the pathologic processes through which the two cases herein reported passed. Hallé has given intensive study to the subject ever since his first article in 1888, and during the last fifteen years he has selected for special investigation 200 cases of chronic tuberculous renal infection, 100 from autopsy and 100 from nephrectomy, and from this material he has drawn conclusions that simplify our understanding of the modes and stages of the pathology of renal tuberculosis.

Briefly, chronic renal tuberculosis is divided by him into three types:

1. Primary closed parenchymatous tuberculous nephritis.
2. Primary open tuberculous pyelitis, or pyelonephritis.
3. A mixed type of the above two varieties.

In the first, the primary closed parenchymatous tuberculous nephritis, the infection is situated in the parenchyma, most frequently in the cortex, it is limited, and easily encapsulated; the peripherally growing lesions progressively involve the poles and lobules, forming cold abscesses, and end by a closed cavernous parenchymatous tuberculosis with one of two ultimate conclusions—liquefaction or caseation. The lesions may be multiple and as the condition progresses and the entire kidney becomes

involved, secretion ceases. Interstitial pelvic inflammation ultimately destroys this portion of the organ and its area is replaced by a fibro-lipomatous degeneration and scar tissue. The condition ends by "total, successive, or simultaneous, exclusion of the kidney," or "spontaneous nephrectomy." Time simply adds atrophy to the process. Hallé found 36 such cases from the autopsy series and 30 from the operative series.

In the second type, the primary open tuberculous pyelonephritis, the infection originates in the tissues of the renal pelvis high in the calices and the papillo-calicular sinuses. It occasions a progressive ulceration working up into the renal tissue from the lateral surfaces of the papillae. Deeper lesions may develop but the calicular lesions are always the more advanced, and the infection remains essentially a tuberculous pyonephrosis. Of this type there were found at autopsy 35 specimens, while from nephrectomy only 24 were obtained.

Hallé's third type is a mixed one where both of the above processes are co-existent, and he found 20 such examples from the autopsy series, while from nephrectomy there were obtained 42 specimens. These figures show that the mixed type is by far the most frequent clinically and that the pure types, one and two, are of about equal occurrence post mortem. There were a few aberrant cases not classified. He further elaborates that type one is essentially hematogenous in its origin, that type two is lymphogenous, while type three is again mixed, or that the pyelitis is secondary to an older parenchymatous lesion, either by direct descent or by recurrent infection from a lumbar adenopathy.

Accepting the above as the simplest statement of the pathology of chronic tuberculosis of the kidney, let us turn our attention to the consideration of the state spoken of as "closed tuberculosis." This may take place from one of two different causal lesions, either that the obliteration of the ureter has prohibited the kidney from emptying its pathologic products into the lower urinary tract, or that the destruction of the kidney secretory tissue has taken place alone, or at relatively the same time, with the obliterating ureteral lesion. The result in either case is

the functional exclusion of the affected organ. These two processes correspond to the above outlined pathologic states, and while in the former—(primary ureteral obstruction)—there follows a secondary destruction of renal tissue, it is also associated with the products of renal retention and the formation of a tuberculous pyonephrosis, whose character may vary within wide limits as to size and symptoms. In the latter group, however, where the infection is primary in the parenchyma, secretory production is at a standstill before occlusion of the ureter occurs, and there is left a caseous mass whose final disposition depends upon gradual atrophy and absorption. This latter group forms the so-called “silent kidneys” and it can be readily appreciated that it is only in them, where functional disappearance of the organ is the primary step and pelvic and ureteral occlusion the secondary one, that you can hope to have such a thing as symptomless autonephrectomy. In such a case there is no tumor, no distention to cause pain, no reason for local symptoms of an alarming character, and with the complete occlusion of the ureter any vesical lesions that were present can be expected to heal as after a surgical nephrectomy. And it is from this small group of favored few that I wish to report two cases. In the first the condition is simply one of closed renal tuberculosis of the primary parenchymatous type, the kidney was obtained by nephrectomy and the condition is not healed, and I present it more for the fact that it illustrates the early stage of the road toward healing, of which the second specimen obtained at autopsy is probably a remarkable example.

The knowledge of the interesting evolution of renal tuberculosis toward symptomatic clinical cure by this exclusion, or closing off, of the infectious process does not need proof, as its surgical pathology has already been established by the works of Tuffier, Hallé and Motz, Guinon, Bonneau, Harbitz, Smirnow, and others, while isolated cases of closed tuberculosis of the kidney have been reported by Keyes, Fowler, Heitz-Boyer, Elkhorn, Delbet, Zuckerkandl, Gallavardin and Rabattu, Kelly and Burnam, Bernard and Patel, Paviot and Delachanal, LeFur, Rihmer, Kapsammer, Ehrenpries, Cabot and Crabtree, Wald-

schmidt, and probably a few others. Some of these are clinical cases studied over a number of years, oft-times they have been followed during and through their acute renal infection, the diagnosis of a unilateral tuberculous lesion being made at the time; then because of the refusal of the advice for operation, or for other reasons, the surgeon has had to be contented to follow the case, has seen the symptoms abate and finally disappear, while in all reported instances subsequent operation, or autopsy, has shown a kidney entirely destroyed by the infectious process, and now but a shell of capsular tissue enclosing some cavities filled with caseous material, the well named "massive degeneration" by Tuffier.

There is little doubt that the infectious character remains present for some time after complete destruction and ureteral closure has taken place. This has been demonstrated by the study of the cases of Bonneau, Tuffier, Tilden Brown, Ehrenpries, Kurlow and Green, who have individually shown either the tubercle bacillus in the caseous contents of the kidney sack, or typical tubercle formation in the remains of the kidney or ureteral tissue, and in one case bacilli from within the core of a calculus present. But as the caseous mass gradually becomes more inspissated it continually undergoes absorption and atrophy, until there must come a time, if the patient lives, when we can truthfully speak of the condition as healed, and the infectious process proved to be at an end. There is the drawback that the absence of the proof of activity must be taken for the proof of cure. Lawrason Brown says, that "the tubercle bacilli were exceedingly rare in the kidney sack, or indeed may have entirely disappeared," and I believe it can be truthfully stated that the absence of tubercle bacilli and typical tubercle formation can properly be taken for the assurance of an actual healed lesion as the pathologic process is not simulated by any other lesion that we know of.

Two other points remain to be mentioned as illuminating these cases. First as regards the origin of the tuberculosis. In a small group of cases, it has been assumed that the infection was primary in the kidney and limited to it alone. Clinically this

is not infrequent, anatomically it is very rare. Walker concludes that several of his cases must have been primary in the kidney. Waldschmidt, on the other hand, in 40,631 autopsies found chronic renal tuberculous in 119 cases, and in only one was there no other tuberculosis elsewhere in the body: and again in 100 nephrectomized patients, 44 of whom were known to have other tuberculous foci at the time of operation, he was able to trace 14 of the remaining clinically primary renal cases through their post-mortem examination at a later date, and again there was only one who was entirely free of other tuberculous foci. That such primary involvement is rare needs no further special mention.

The second point is the actual cause of death. A patient with a closed renal tuberculosis does not die essentially from his renal disease. It has been demonstrated, both by clinical cases after nephrectomy and by autopsy findings, that the majority of them ultimately succumb to tuberculous lesions in other parts of the body. This is the usual rule. In a small group death has been due to chronic nephritis and uremia, attention to which has been called by Harbitz, Albarran, Gallavardin and Rabattu, Karo, Heitz-Boyer, Oraison, and Israel. In such cases the renal insufficiency is probably caused by the increased load thrown upon the remaining kidney, itself free from tuberculous disease, but suffering chronic interstitial changes from the toxemia due to the other focus of infection.

And finally it is here that we approach a rare group of exceptional cases; fortunate individuals *in whom* the tuberculous infection has been primary in one kidney; *in whom* the infection has been controlled by nature to the exclusion of any further involvement; *in whom* this local kidney infection has been ultimately conquered; and *in whom* death, when it came, was due to an entirely extraneous cause. The literature is extremely small. I would like to mention Rafin's cases, where in his study of 74 patients with unoperated renal tuberculosis he reports that 4 died of some other disease, enumerating cancer of the stomach, pneumonia, peritonitis, and "sudden death," as being the diagnoses of their medical attendants, but from his report there were apparently no post-mortem examinations.

Albarran in 1899 was able to collect only 5 instances recorded in the literature, where the patient died, with a tuberculosis limited to one kidney, and where death was due to some entirely extraneous disease. He admitted to this category only the cases of Golding Bird, Bardenheuer, Czerny, Beaver, and specimen no. 427 Musée Guyon. Waldschmidt in 1912 records another authentic case. Unquestionably it is here that we must look for the confirmation of the possibility of spontaneous healing of advanced renal tuberculosis, and in presenting the second of my two cases, I feel that in it is found another instance of such spontaneous healing of renal tuberculosis, death being due at a much later date to pernicious anemia.

Case 1

J. G., age twenty-seven years. Entered the Urological Service of Dr. T. R. Neilson, University of Pennsylvania Hospital, August 27, 1917.

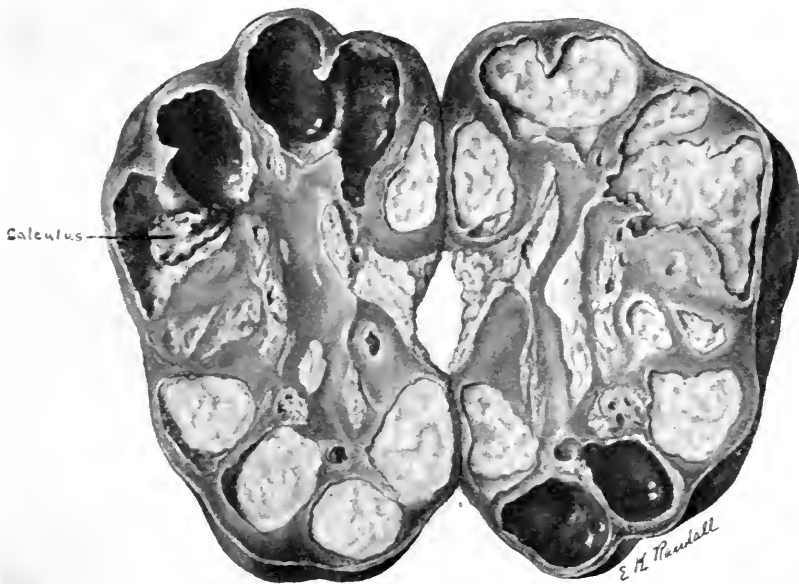
Patient complained of constant dull pain in the right loin, with slight radiation downward to groin. Pain at the end of micturition, and in rectum.

Past history. Patient is single, a cooper by trade. Mother living and well. Father died at the age of thirty-six years of consumption. He has never had a serious illness since childhood. Nine years ago he had an urethritis, and at the same time a small sore on the glans. There were never any manifestation of secondary rash, though he had a bubo form on the left side which was opened. No history of cough, or expectoration, no night sweats, though six months ago on one day he spat about one teaspoonful of blood. For the past five months he has had an increasingly hoarse voice. Appetite is not so good; bowels are regular. Five months ago he had some pain in his right chest which lasted for two or three days. Has not noticed any elevation of temperature.

Present illness. The patient came to America four years ago, and three weeks after his arrival his present complaint began. Urination was painful especially at the end of the act; two years ago he had terminal hematuria for a period of two weeks, urination at this time was frequent and urgent. In 1915 he was in a hospital where operation was advised and attempted but the patient took the ether so badly

that it was given up. Subsequently he was three times in another hospital where he was told that the disease "was sleeping" and would be made worse by an operation. In the present year he was in still another hospital where he was first told that he had tuberculosis of the kidney. Four years ago he weighed 170 pounds; at present he weighs 131 pounds.

Physical examination. Rather poorly nourished and pale adult male, with a very hoarse voice. Head, ears, eyes, and mouth are normal, some pyorrhea.



CASE I. AUTONEPHRECTOMY (RIGHT): COMPLETE DESTRUCTION OF THE KIDNEY WITH OBLITERATION OF THE PELVIS AND URETERAL OCCLUSION

Chest: Dr. Miller. Chest symmetrical with slight depressions above and below clavicles. Expansion good and equal. At both apices there is slight harshness of breathing and a little impairment to percussion, but there are no râles. Probably this indicates a quiescent tuberculous infection but there is no evidence of activity at the present time. Do not think his pulmonary condition a contra-indication to an operative procedure.

Heart: No abnormality.

Abdomen: Soft and relaxed, rather scaphoid, no palpable mass, right kidney region slightly tender on deep pressure and the lower pole is palpable. Left kidney is neither tender nor palpable.

Extremities: Normal.

Laryngeal examination: Dr. Husik. The patient has a tuberculous larynx. Infiltration of right vocal cord overlapping true cord. True cord not visible. Infiltration of the inter-arytenoid space.

August 29, 1917. Wassermann: Negative.

Urine examination: Amber, floccular sediment, 1015, light cloud of albumin, few hyalin casts, many white blood cells.

August 30, 1917. Blood count: R. B. C., 4,650,000; W. B. C., 9,360; hemoglobin, 84 per cent.

Differential: Polynuclears, 71 per cent; lymphocytes, 22 per cent; large mononuclears, 3 per cent; transitionals, 2 per cent; eosinophiles, 2 per cent.

September 3, 1917. Cystoscopy: Drs. Pelouze and Randall. Patient quite tolerant to cystoscope and with a normal bladder capacity. No active ulceration and no general or localized congestion. No stone or tumor. Left ureter normally placed and functioning actively at regular intervals, excreting clear urine. Right side of trigone appears atrophic and pale. Right ureteral orifice appears as a dimple at the upper cornu of the trigone, slightly drawn and retracted, cannot be seen to functionate. Catheter passes up left ureter to pelvis without meeting any obstruction, kidney actively secreting. Catheter cannot be made to even enter right ureteral dimple. Diagnosis: Closed right renal tuberculosis.

September 7, 1917. Cystoscopy: Dr. Randall. Garceau occluding catheter placed in the left ureter for 10 cm. Phenolsulphonphthalein test: 6 mgm. intravenously, appeared in eight minutes. First fifteen minutes secretion, 34 per cent; second fifteen minutes, 20 per cent. Fluid drained from bladder, consisting of irrigating fluid plus right kidney secretion contained no phenolsulphonphthalein. Conclusion closed right ureter, compensatory functional hypertrophy of right kidney.

September 9, 1917. Total phenolsulphonphthalein function test: 6 mgm. given intravenously, appeared in seven minutes. First hour, 60 per cent; second hour, 15 per cent.

September 10, 1917. Cystoscopy: Drs. Randall and Pelouze. Injection of indigo-carmin intramuscularly appeared from left ureter in

seven minutes and in three minutes was in greatest intensity, none from right ureter in twenty-three minutes observation.

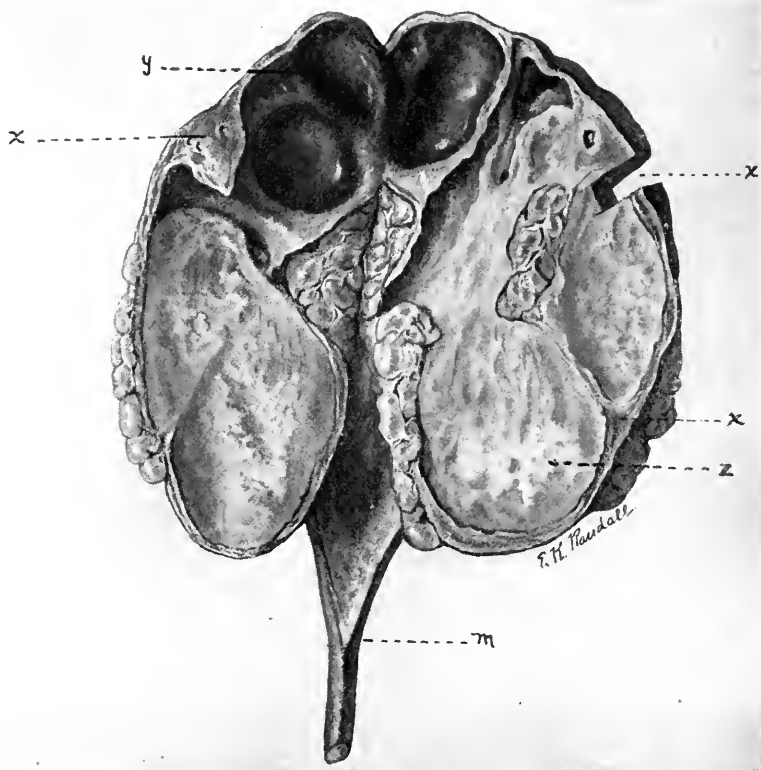
September 12, 1917. Operation: Dr. Randall, assisted by Dr. Cheney. Right nephrectomy. Very little perirenal adhesions. Pedicle clamped and organ removed without difficulty and without soiling the wound. Ureter could not be isolated or demonstrated at any time during the operation. Pedicle ligated; wound closed about one small tube drain which was removed on the seventh day and healing was practically per primum.

September 28, 1917. Discharged from the hospital. Wound completely healed. To be sent to state tuberculosis sanatorium as soon as vacancy can be obtained. Specimen placed in Kaiserling's solution without opening it, to prepare it for mounting. When fixed it was sectioned and showed as illustrated a series of completely broken down sacs filled with a semi-solid or caseous mass. The renal pelvis is completely organized and filled with a fibro-lipomatous tissue. The ureter is simply a quill-sized fibroid band on the back of the specimen and is without lumen. In the posterior, or left-half of the specimen and situated in the upper half is a calculus of 3 by 1 cm. in size. Macroscopically there is no tissue of secretory power in any part of the kidney.

Discussion. This case illustrates the final step in the destruction of a kidney by tuberculosis, when that infection has its origin in the parenchyma of the organ, with a complete reduction of the secretory tissue to a caseous mass. During the course of this destructive process the infection has passed to an involvement of the excretory passages, and for a while the patient suffered all the symptoms of an acute tuberculous cystitis. With the complete destruction of the secretory tissue the organ ceased to empty its pathologic products into the lower urinary tract, the lesions of the ureter healed and in so doing obliterated its lumen, the renal pelvis was organized into a mass of fibro-lipomatous tissue, the cystitis healed. It is a case of closed renal tuberculosis, a case of auto-nephrectomy, the one step that nature does take towards a spontaneous exclusion of such an advanced renal infection. Clinically the patient has gained 14 pounds in two months.

Case 2

E.K., age forty-seven years. Single, carpenter, American; was admitted to the Philadelphia General Hospital, June 3, 1916, and died there June 20, 1916, with a diagnosis of pernicious anemia. His past medical history gives malaria as his only previous illness. On ad-



CASE 2. AUTONEPHRECTOMY (RIGHT). MASSIVE DEGENERATION OF KIDNEY, OCCLUSION OF URETER; ATROPHY AND PARTIAL ABSORPTION OF THE KIDNEY REMNANTS

X = areas used for tissue study; Y = material for pig injection; Z = caseous material almost entirely absorbed and replaced by scar tissue; M = occlusion of ureter.

mission he stated that his present complaint was sudden in onset four weeks ago with a complaint of loss of breath and pain over the cardiac area. There has been a gradual loss of weight and strength, some

slight cough and expectoration, dyspnea, and pain in the chest. Two weeks ago he had a profuse nose-bleed and ten days ago a hoarseness of voice appeared.

Physical examination. Fairly well developed, marked anemia, and slight emaciation.

Head and neck: Are negative.

Chest: Not proven tuberculous, but suspicious over left back and right apex.

Heart: Apex beat displaced slightly to the left, rough systolic murmur, distinct at apex slightly external to the midclavicular line.

Abdomen: Liver dullness normal and remainder of abdominal contents negative.

Extremities: Fingers are normal; legs are covered with disclosed areas of old healed scars.

Patient is in a very weakened condition.

Nose and throat: Specialist's examination. Atrophic rhinitis, ulceration of the septum, thick crustations on uvula and both vocal cords. "Condition probably specific origin or due to extreme mal-nutrition." (Note—It has been impossible to find out what the above word "specific" was intended to convey.)

June 4, 1916. Urine: Amber, acid, 1030, marked trace of albumin, leucocytes, urates, epithelium.

Sputum: Negative for tubercle bacilli.

June 6, 1916. Wassermann: Negative.

Blood pressure: Systolic, 142; diastolic, 110.

June 7, 1916. Urine: Amber, acid, 1012, granular casts, few leucocytes, epithelium, triple phosphates.

Blood: Hemoglobin, 35 per cent; W. B. C., 9,400; R. B. C., 2,229,000.

Coagulation time: 11 minutes.

Differential: Polynuclear neutrophiles, 81 per cent; small mononuclears, 7 per cent; large mononuclears, 11 per cent; basophiles, 1 per cent; normablasts, 8 cells; megaloblasts, 17 cells; poikilocytes, Yes.

June 8, 1916. Sputum: Negative second time for tubercle bacilli.

June 9, 1916. Sputum: Negative third time for tubercle bacilli.

June 10, 1916. Nose and throat being irrigated with normal saline solution and patient seems much better.

June 13, 1916. Blood count: Hemoglobin, 37 per cent; polynuclear neutrophiles, 92 per cent; small mononuclears, 8 per cent; normablasts, 2 cells; basophile megaloblast, 4 cells; granulations, Yes; poikilocytes, Yes.

Vocal cords: Are better.

June 14, 1916. Stool negative for ova or parasites. Occult blood: Negative.

Blood coagulation time: Nine minutes.

June 17, 1916. Patient had a hemorrhage from the bowel at 10:15 a.m., passing about a quart of blood.

June 18, 1916. Patient had four more hemorrhages from the bowel, losing at least another quart of blood. He was in coma until about four o'clock in the afternoon, when he became very restless and was given $\frac{1}{4}$ grain morphia hypodermically, and an ice bag to the abdomen.

June 20, 1916. Patient died today.

The temperature chart shows that the temperature was sub-normal from the time of admission until June 16, it then began to rise slowly and only touched 100.2° before death. Pulse and respiration chart shows nothing abnormal.

Post-mortem examination (abbreviated). Autopsy performed by Dr. B. H. Lucke, June 20, 1916.

Clinical diagnosis: Pernicious anemia.

Pathological diagnosis: Primary anemia, hypertrophy of heart, chronic interstitial myocarditis, slight sclerosis of the mitral valve, pulmonary edema, chronic interstitial nephritis, tuberculous cystic degeneration of the right kidney with obliteration of the ureter, cysts of unknown nature of pancreas, atheroma of the aorta.

Head: Negative, lips and sclera pale.

Chest: Muscles pale; pericardium normal; heart no gross lesions. Aorta slightly atheromatous at its beginning.

Lungs: Both adherent at the apices. No areas of consolidation. Cut surface of left lung even, grayish, red color, with large amount of frothy blood-tinged fluid exuding on moderate pressure. Bronchi and bronchioles throughout of normal character. Peribronchial lymph nodes of normal size, marked anthracosis. No macroscopically healed lesions of tuberculosis. No active lesions. Right lung is similar to the left.

Abdomen: Peculiar lemon yellow color to abdominal fat. All organs in their normal place. Spleen normal. Liver normal. Left kidney embedded in thick layer of fat; capsule adheres in many places. On stripping capsule the surface is left coarsely granular and of light brown color, on which numerous retention cysts stand out prominently. These cysts are filled with a gelatinous light straw-colored material. The organ is increased concentrically; cut surface light brown, cortex

different shade from the medulla and can in no place be recognized clearly. Throughout kidney substance are numerous cysts filled with gelatinous material. Pelvis filled with yellow fat. Adrenal is normal.

Right kidney: It is embedded in the same thick layer of fat. Measures 8 by 5 by 5 cm., and consists almost entirely of a cyst filled with white cheesy material, which looks and feels like white clay mixed with mucilage. There is no visible secreting substance left. The ureter on this side is open for ten centimeters and comparatively thick walled, below this point it is entirely occluded.

Pancreas: 19 by 14 by 2 cm. Color pale yellowish brown; somewhat firmer than normal. Cut surface is firm. Middle portion of organ contains several yellowish rather firm areas, which upon section are found to be cystic with firm fibrous walls. These cystic masses are about one cm. in diameter and altogether three were found.

Stomach: Some sub-mucous hemorrhagic areas.

Intestine: Large and small are normal with a very pale mucosa.

Bladder: Walls tough and fibrous, mucosa reticulated.

Bone marrow: From right tibia is lemon yellow in color.

Study of right kidney specimen. Dr. Robert Keilty. Sections for microscopic study were made from three different parts of the kidney mass where it was thought either elements of normal kidney structure, or lesions of tuberculosis may still be present. These were stained by the usual methods for tissue study and showed a complete absence of normal kidney tissue, or any secretory tissue whatever. There was nowhere to be found any tissue changes suggestive of tubercle formation. Other sections were cut from the same blocks of tissue and stained for the presence of tubercle bacilli; they were consistently negative. Sections similarly studied were taken from the ureteral wall and were likewise negative. Smears were made from the caseous material taken from various parts of the specimen and stained for the tubercle bacillus; they were persistently unproductive and negative. An emulsion of the caseous material was injected into guinea-pigs with similar negative results.

Discussion. In analyzing this case fairness calls that attention be drawn to possible errors in the diagnosis and study.

In the first place, I think that no question can be raised in regard to the fact that the patient had pernicious anemia, and died of it. The complete blood studies confirm this beyond peradventure.

Secondly, it is to be regretted that his past history is so incomplete; it is the result of an equally pernicious custom, where the history blanks are printed questions, or lists of diseases, or symptoms, which the interne has but to underline or erase.

Thirdly, we find an examination by a laryngologist, where the condition is attributed to either "specific origin, or due to extreme mal-nutrition." The meaning of this word "specific," can not be traced to the man who used it; the patient on entrance was admitted to the ward for tuberculosis, if that is meant, the repeatedly negative sputum examinations should exclude that diagnosis. If on the other hand it was meant to convey its usual interpretation, i.e., syphilis, the negative Wassermann test would preclude that diagnosis. It is more probable that the second deduction, that it was due to "extreme mal-nutrition," was the correct one, in that the condition improved so promptly under normal saline application, and hospital nursing alone.

Fourthly, it is to be regretted that the autopsy examination did not include the examination of the larynx.

Fifthly, it might be raised that the cystic condition found in his pancreas and the cysts in the left kidney might be tuberculous in origin; I can not gainsay this except to state that if so the sections demonstrated this to be non-active and devoid of the usual evidence of tuberculous process.

Sixthly, I can but state in regard to the condition of the apices of the lungs that careful search failed to demonstrate any typical tuberculous lesions, other than those almost routinely found in every adult body and ascribed to the trivial infections of early life. There certainly were not any active or healed lesions that would allow of the assumption of a possible pulmonary involvement at an earlier date.

CONCLUSIONS

In the past it seems that it has been the aim of everyone to prove the incurability of renal tuberculosis, whereas if we were constructive, the harder problem would appeal to us, and we would more probably seek to establish the possibility of cure by anatomic healing. I feel that in reporting this second case, I have

recorded one where renal tuberculosis was not only primary, but was unilateral, that it was likewise completely destructive of the organ, that spontaneous "autonephrectomy" succeeded, that the infectious character was ultimately conquered, and that the patient succumbed to a disease, in no way related to his renal catastrophe. The interest that the first case bears to the second is that it but represents the renal change through which, as one stage, the second must have passed, and it is incorporated in this report as conclusive evidence, that in the second case the pathology is that of tuberculosis, even in the absence of tubercle bacilli, or tubercle formation, their absence being essential to the conclusion, that the lesion is healed.

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MIGRATING BLADDER STONE

B. S. BARRINGER

New York

Some months ago a patient, about fifty years old, came to Bellevue Hospital and upon making a rectal examination I found just within the anal sphincter a stone nearly as large as a hen's egg. An attempt was made to remove it but we finally had to put the patient under ether to do so. It was grasped by a large stone forceps and considerable force was necessary to extract it. The stone was black, rough and shining like coal. The patient's history was as follows:

Twelve years before he had a perineal section and perineal drainage, the exact reason for which I could not ascertain. Urethral sounds were subsequently passed. Ten years ago he entered a hospital because of partial retention of urine, dribbling and abscess formation in the perineum. He was told that he had a growth in the rectum because of marked constipation and straining at stool. Another perineal section was performed. Ever since this last operation he has noted at intervals the escape of urine from his rectum and fecal matter from his urethra. For the past six months this has been constant with great urinary tenesmus and very often fecal and urinary incontinence. He has had the sensation of some obstruction and dull pain in his rectum and has noted that his stools were ribbonlike. A year ago he again went to a hospital for an abscess in the perineum. This was opened by a house officer who subsequently passed sounds and the patient was discharged. As far as we can ascertain he never had a rectal injury, and never had introduced any foreign body into his urethra. He had an attack of gonorrhea at the age of twenty-one.

The patient had, in summary, a history of illness for twelve years—had had three operations and complained of the passage

of urine by rectum and feces by urethra, much pain and great loss of flesh and strength.

The examination of the stone by Dr. Ewing revealed the following:

It has as a nucleus a piece of the shaft of a long bone, probably human, 1.5 cm. long by 0.5 cm. wide. The identification is based on the presence of bone structure identified under the microscope. One finds Haversian systems, lamellae of bone, stellate bone cells in orderly concentric and parallel arrangement. The bone seems to have been slightly softened but cuts or chips with great difficulty. What changes it has passed through are not clear, but I know of nothing in nature which presents the structure shown by this material except bone. It looks like bone in the gross. The piece has been sawed at both ends.

This center nucleus is surrounded by lamellae of phosphatic crystals in which no fecal matter is found except in the way of slight staining. This clearly indicates that the stone arose in the bladder.

Whence came the bone is a mystery. Subsequent to taking out the stone the patient vastly improved locally and generally and when he left the hospital no fecal matter came through the penis and but a few drops of urine were passed rectally. He urinated six to seven times a day, and two to three times at night. There was no urgency. Sounds up to 29 passed easily. There was, I regret, no cystoscopy. With the source of the bone and the time of the passage of the stone from bladder to rectum veiled in mystery, one thing is clear—that the presence of the rectal stone caused the vesico-rectal or a urethro-rectal fistula to persist and its simple removal caused such a fistula to very nearly heal, and caused an extraordinary change in the patient. He left the hospital vastly improved in weight and strength.

A METHOD FOR THE CONTROL OF HEMORRHAGE AFTER SUPRAPUBIC PROSTATECTOMY

B. S. BARRINGER

New York

The following method has been used to control bleeding in some fifty cases of suprapubic prostatectomy for carcinoma and adenoma. After enucleation of the prostate a strip of 2-inch gauze some yards in length is inserted through the open bladder into the bed from which the prostate has been removed. The gauze is packed into the prostate bed with the index finger of the right hand, or with a plain thumb forceps, against the counter pressure of two fingers of the left hand which have been previously inserted into the rectum to aid in enucleating the prostate. Enough gauze is used to overfill the prostate cavity. With the hemorrhage controlled a simple sponge stick is passed into the bladder and the gauzed ball grasped by this. The bladder is now sutured to the rectus fascia and the hole in the bladder sewed up, simply allowing space for the gauze and sponge stick. No tubes are put into the bladder, but the urine finds exit alongside the sponge stick and gauze. The dressings are changed as often as they are saturated. If the bleeding begins again, pressure on the sponge stick controls it.

Packing has long been used to control the hemorrhage after prostatectomy. Before I used a sponge stick attached to the packing, which is the only original item claimed in the above method, I occasionally have had to repack the prostate cavity in order to control bleeding.

This repacking, perhaps some hours after the operation, is very hard on the patient and certainly does not add to his chances of recovery. The sponge stick has done away with the necessity for repacking; the sponge stick is removed from the bladder in twenty-four hours, and the packing in forty-eight hours. A

suprapubic tube may then be placed in the bladder, or, as has been my custom lately, no tube at all is used, the wound being frequently redressed with dry sterile gauze. In placing the packing in the bladder especial attention is paid to the posterior lip of the torn prostate sheath. Keyes and others have pointed out that the severest hemorrhage is likely to come from here. The packing is pressed down hard against this lip. The advantages of this method are:

1. It is rapid, so differing from many other methods, most of which probably controlled hemorrhage but took too much time doing so.

2. No special instruments or devices are used. Packing and a sponge stick are always at hand.

3. It stops hemorrhage which may occur both at the time of operation and after operation.

The disadvantages are: (1) The patient keeps wet, the urine simply seeping alongside the packing, and so out. Frequent changes of the abdominal dressings are necessary to keep the patient comfortable. (2) The packing in the prostate cavity causes a certain amount of pain and tenesmus. This is controlled by morphine.

One of the alleged disadvantages that has been suggested is that the pressure of the packing upon the lower portion of the ureters might cause stoppage of the urinary flow. A very grave disadvantage if true. In none of my cases has there been any suggestion of a temporary anuria or even oliguria. The dressings have always and pretty promptly become urine soaked. Dr. Keyes has had one case in which the kidneys refused to function until the packing was removed. This may have been reflex and might have happened had not packing been used. I simply report it.

I am not at all sure that this method stops hemorrhage more effectively than the Hagner bag. I regret to say that I have not used this ingenious device and cannot therefore judge of the relative merits of the two. Theoretically at least gauze packing should promote clotting of blood better than a smooth rubber surface. In my hands the method has proved to be both rapid and effectual in controlling the bleeding after prostatectomy.

A CASE OF BLASTOMYCOSIS INVOLVING THE PROSTATE AND SEMINAL VESICLES

FREDERICK J. PARMENTER AND BURTON T. SIMPSON

Buffalo, New York

Blastomycosis is a relatively frequent disease, especially in Chicago and its immediate neighborhood, though sporadic cases have been found and reported in all parts of the United States.

Buffalo seems to have had a relatively large number of cases, as Dr. Grover Wende states in a verbal communication that he personally has seen at least twenty-five but has never reported them, and that most of the infections occurred in individuals living in and around Buffalo who had never resided in the middle west; this may be easily true of other sections of the country.

The disease is a very fatal one, in which the skin or lungs seem to be primarily involved, with a gradual extension to other structures as muscles, bone, liver, kidneys, spleen, pancreas and brain; the patient dying from sepsis.

In studying the cases reported in the literature but little attention seems to have been directed to the urinary tract, and although the autopsy reports show renal involvement in nearly all cases, the clinical records of these patients show that the urine was normal in nearly all instances; no mention was made of any urinary symptoms, i.e., frequency, urgency, difficulty, etc. In one case pus was reported present without other symptoms, the pus originating in a prostatic abscess found at autopsy.

Wade and Bel¹ in 1916 tabulated all cases reported to date with their clinical and autopsy data. In the series of forty odd, involvement of the prostate was found three times, of the epididymis alone once, and of both prostate and epididymis together once. In none of these cases was the diagnosis of prostatic

¹ A critical consideration of blastomycosis. By Wade, Windsor H. and Bel, Geo. S. Arch. Int. Med., xviii, 103, 1916.

blastomycosis made during life, or if it were no record of the fact was made. As noted above, pyuria was noted clinically once but no report of its origin was made until autopsy.

Krost, Moes and Stober² report a case with the autopsy finding, in which the organism was found in the urine during life but its exact origin was not determined. The autopsy showed both the kidney and prostate to be the site of many blastomycotic abscesses.

The case to be reported presented such extensive involvement in so many different structures of the body, with apparent recovery under treatment, that a detailed account of the disease as it affected this man, together with the unusual involvement of the prostate and seminal vesicles, should be of interest.

The patient was referred to the writer May 1, 1918, by Dr. Grover Wende, under whose care he had been for blastomycosis of the skin. Dr. Wende had made a tentative diagnosis of prostatic blastomycosis because of his urinary symptoms.

The patient was forty-four years of age, married, but not living with his wife. There was one child, a girl of eighteen, who was perfectly well and healthy. He had resided in Chicago for sixteen years, where the disease developed and had continuously followed the occupation of tinsmith. His previous health had been excellent except at the age of seventeen when he felt tired and weak for several months but soon recovered. At the age of twenty-six he suffered for twenty weeks from an electric burn of the chest, right hand and heels but recovered completely at the end of this time. The patient had always been troubled with catarrhal headaches (sinusitis); aside from which his past history was negative. Venereal history was denied.

The present illness began in September, 1914, with a cough which persisted in spite of treatment. At this time his health began to fail gradually and his weight, which was 157 pounds, began to decline, so that in February, 1915, six months after the onset of the cough, it had reached 132 pounds; his general condition was extremely serious. About this time a profuse muco-purulent blood-tinged expectoration developed, together with a most extensive skin eruption, most of which

² Krost, Moes and Stober: J. A. M. A., Jan. 18, 1908.

disappeared in a few weeks. That which remained resulted in abscess formation in the following locations: right calf and buttock, wrist, left hip and later on the calf of the leg.

In March, 1915, he entered the Presbyterian Hospital of Chicago, where the diagnosis of blastomycosis was established and the abscesses in which the organism was found, were drained, resulting in marked improvement both locally and also in his lung condition.

In May, 1915, he left the hospital, at which time some of the areas of ulceration had healed, others were indolent, and in still other areas the disease seemed to be slowly spreading. Lesions had also appeared on the neck and face. In the hospital iodides were administered, which would help greatly some of the ulcers and have no effect on others. This bizarre action of iodides upon blastomycosis has been noted by some observers,³ who point out that the drug either helps or does not. The writer has found no mention in the literature of improvement in certain involved areas in a given case following this therapy, while other lesions, both new and old, were uninfluenced by it.

From this time until April, 1917, when he came under Dr. Wende's care, his general health was fair, his cough had disappeared and he gained in weight, but the skin lesions were still present, especially on the face and neck.

Upon therapeutic doses of x-ray the lesions began to heal quite rapidly, and by fall all evidences of the disease had disappeared.

The urinary trouble began in October, 1917, when an attack of frequency, urgency, burning and difficulty in urination suddenly occurred, lasting about twelve hours; after which he felt all right. There was a recurrence of these symptoms in January, 1918, lasting a week; and a third attack in March, 1918, the symptoms of which, though greatly ameliorated, are still present.

Examination showed a man normally developed and well nourished. The skin of the face, neck and right leg was extensively scarred. His heart, lungs and abdomen were negative, as were the throat, teeth, pupils and reflexes. The breath had a rather earthy odor, which is suggestive of actinomycosis. Urological examination: Glasses 1 and 2 were both very small in amount, cloudy, blood-tinged, and contained many small prostatic shreds.

³ Report of a case of blastomycosis. By Krost, Stober and Moes. *Arch. Int. Med.*, xiii, 567, 1914.

Rectal examination showed a dense infiltration of the prostate, seminal vesicles and Denonvillier's fascia, associated with considerable edema which had obliterated all anatomic outlines, and suggested an inflammatory rather than a malignant process. Upon massage blood only was obtained.

Cystoscopic examination showed the bladder capacity diminished about one-half; the mucous membrane of the upper half, *i.e.*, the dome and sides, was normal, while the lower half, including the area around the ureteral orifices, trigone and sphincter showed marked bullous edema.

The ureters were not catheterized, but the urine coming from both ureters was clear, and the voided samples so small in amount that the cloudiness was thought to be due to the prostatic and seminal vesicular involvement, which was borne out by the subsequent progress of the patient.

The posterior urethra, together with the verumontanum was acutely inflamed, bleeding easily; some of the prostate ducts were closed, others open and filled with muco-purulent secretion. Some of this material was collected under as aseptic precautions as possible for examination, but no yeast organisms were found.

After the examination the patient returned to his home in a nearby town and was not seen until May 12, 1918. At this time rectal examination showed that the edema had largely disappeared, so that some idea could be gained of the relations of the prostate and seminal vesicles. The right prostate lobe could be fairly well outlined and was rather nodular, quite hard and sensitive. The urine was clearer, the blood less, and his symptoms greatly improved. A 22 French sound was passed, and 2 cc. of 1 per cent silver instilled in the posterior urethra with a Keyes-Ultzman syringe.

On May 25, 1918, the edema and exudate in and around the seminal vesicles was greatly reduced, the vesicles feeling much softer, and the prostate easily outlined. The suburethral portion was so prominent and hard that a calculus was thought of, which however was disproved by x-ray. The secretion was again submitted for examination but was negative for blastomycosis. His symptoms continued to improve.

On June 5, 1919, the urine was clear and the infiltration around the seminal vesicles had disappeared; the right prostate lobe was smaller and the suburethral portion had reached practically a normal size. There had been some return of bladder symptoms, which the patient ascribed to his resuming iodide of potash which he has taken at stated intervals since the beginning of the disease.

On June 24, 1918, local conditions were about the same; and the bladder symptoms had disappeared after discontinuing the iodide. The material secured from the prostate and seminal vesicles for examination showed the typical organism of blastomycosis, which will be fully described by Dr. Simpson in the second part of the paper.

As the local examination showed the disease to be practically stationary the use of the x-ray through the peritoneum was suggested to Dr. Wende; this seemed rational in view of the fact that the skin lesions although resisting all other methods of treatment, had promptly and permanently responded to x-ray therapy, there being no recurrence in over a year.

Local improvement continued rapidly, and by July 24, 1918, the prostate and seminal vesicles felt perfectly normal and all blastomycosis organisms had disappeared from the secretion.

In December, 1918, an acute epididymitis suddenly developed on the right side, which subsided within two weeks, leaving the epididymis, however, swollen and hard. The patient gave no history of former or recent venereal disease and on examination at this time definitely eliminated the possibility of gonorrheal epididymitis. In view of the former findings in the prostate and seminal vesicles, it seems probable that the condition was blastomycosis of the epididymis.

There has been no relapse in any of his former lesions from that time until the present, April 16, 1919, and the organisms have not been found during repeated examinations, the secretion expressed being a clear watery fluid, containing only an occasional epithelial cell and leucocyte; all other prostatic and seminal vesicular elements being absent, the result probably of the action of the x-ray. The epididymis was still large and hard but decidedly less so than on the previous examination.

The x-ray is being continued, and the patient is taking 450 grains of potassium iodide daily upon Dr. Wende's recommendation. It would seem that the disease had been cured, save in the epididymis; though time will have to determine this.

SUMMARY

1. The patient is one of the few to recover apparently from extensive systemic blastomycosis. Only in the epididymis is there any evidence of the disease after four years, during which time the lungs, skin, muscles of the leg, prostate and seminal vesicles have been involved and recovered.

2. This is the first instance to the writer's knowledge, in which a clinical diagnosis of blastomycosis of the prostate was made and confirmed during life.

3. Because of the frequent involvement of the kidneys, shown at autopsy, in blastomycosis, a more thorough study of the urinary tract is urged, which had been neglected in the past, due, doubtless, to the prominence of the disease in other structures in a patient so ill that urinary symptoms might be overlooked.

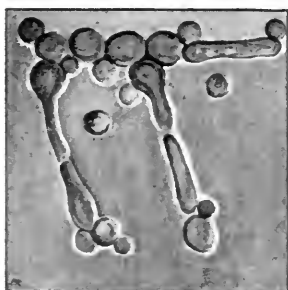
PATHOLOGICAL REPORT WITH A REVIEW OF THE LITERATURE

Busse published the first account of an infection with blastomycetes in 1894, describing a case in which he demonstrated the organisms in the pus and from which he was able to cultivate a pure culture. He classed the organism as a saccharomycete and named the condition saccharomycetes hominis. Several months before Busse reported his case, Gilchrist had demonstrated before the American Dermatological Association, similar organisms in sections of tissue taken from a peculiar skin disease. In later studies by Gilchrist, the organism was identified as similar to the one described by Busse. Soon other cases of similar skin disease were reported in which were found the typical histologic picture and the specific organism.

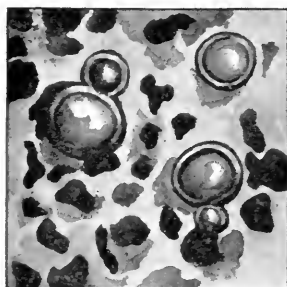
Most of the early cases were localized in the skin and the disease was named blastomycosis cutis. In 1908 Montgomery and Ormsby collected and described twenty-two cases in which systemic blastomycosis was demonstrated beyond question, both by histologic and cultural methods. The majority of these cases had skin lesions and the original infection was probably in the skin, although in a number of the cases, the early symptoms were pulmonary and the respiratory tract might have been the primary point of infection. The mode of extension of the disease from the skin lesions is apparently by way of the blood stream, as lymph nodes are rarely affected. The organism has also been obtained in pure cultures from the blood stream.

The organism was originally classed as a saccharomycete by Busse. Gilchrist and Stokes used the term blastomycete on

account of the budding forms which they found in the tissues. Ricketts, who made an elaborate study of the cultural characteristics of the organism, believed that it belonged to the family of *Oidium*. More recently Whitman has made a careful study of the biologic character of this organism and concluded that it may belong to either the *Hemiasceae* or to the *Euaseae*, being a new genus, which according to DeBeurman and Gougerat might be designated as *Zymonema*. Further studies will no doubt ultimately settle the exact place of this fungus, but at present the most convenient and generally used term is blastomycete.



DRAWING MADE FROM FRESH
SMEAR OF CULTURE



DRAWING MADE FROM CENTRIFUGALIZED
SEDIMENT OF URINE
AFTER STANDING TWENTY-
FOUR HOURS

In the present case the secretion was obtained under aseptic conditions. Microscopic examination of the centrifugized specimen showed round or oval, highly refractive, double-contoured bodies and, in view of the cutaneous condition, naturally these bodies were suspected of being blastomycetes. Accordingly, cultures were made upon glycerine and glucose agar. The urine was allowed to stand at room temperature for twenty-four hours. At the end of this period specimens were taken from the sediment and examined microscopically. In the sediment were found very numerous round and budding forms in all stages from the simple bulging of the protoplasm up to nearly equal bodies which were apparently ready to split off. There were also many mycelial

processes attached to many of the cells. Evidently the organism had developed in the urine which had stood for twenty-four hours at room temperature, for they were much more numerous than in the first examination at which time only the round bodies could be found. Culture tubes were kept in the incubator room on top of the incubator and on the fourth day there appeared smooth round, grayish, moist colonies, which upon microscopic examination showed masses of segmented mycelium. There were also some budding forms. After several days the colonies became confluent, showing a fluffy white growth having fine aerial hyphae. The culture grew into the medium, becoming intimately attached to it. After several weeks, the culture took on a brownish color and became very crumpled in appearance.

The gross and microscopic appearance of these cultures agrees very closely with the results which are to be found fully described in many reports in the literature. In reviewing the literature we were able to find only one case in which the organisms have been found in the urine during life (Krost, Moes, Stober). At autopsy in this case there were found multiple abscesses in the prostate. Churchill and Stober, also, found at autopsy in one of their cases, multiple abscesses of the prostate and succeeded in obtaining the organism from these lesions in pure culture. Lesions of the kidney have been found at autopsy in several cases of generalized blastomycosis but there have been no reports of finding the organism in the urine, in these suspected cases, although attempts have been made to find it.

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NEPHRITIS IN FIFTY-SIX SOLDIERS

HORACE GRAY

Boston

MATERIAL

Place. United States Army Base Hospital 76, Vichy, Allier, France.

Period. Ten weeks from November 12, 1918, to January 21, 1919.

Patients. Total medical ("disease") and surgical ("injury") admissions, 1661. Medical cases, 875, i.e., 53 per cent of the total. Nephritics: After preliminary examination, the men kept for renal observation numbered 56, i.e., 6 per cent of the medical or 3 per cent of the total cases. The source of admission was the Front in 53, and in 3 the Service of Supply (as it happened, base hospital personnel). This nephritic incidence is lower than that reported (1) recently for albuminuria in soldiers, but practically confirms the frequency of 5 per cent reported in a more detailed study of (2) nephritis strictly construed. However it undoubtedly falls below the true proportion of nephritis among enlisted men in the American Expeditionary Forces, as some incipient cases must have been missed, since pressure of other work in the laboratory prevented the desired urinalysis on all medical patients, and permitted it only on those showing suspicious symptoms or signs. This small number of cases furthermore falls below the desideratum for definite conclusions, but their presentation is encouraged by the interesting inferences on even smaller recent groups of 30 cases (3) and 12 nephritic cases (4).

METHODS

Case records. On all patients systematic notes were kept. Family history, past history, habits, present illness and physical examination were recorded on forms like table 1, which had

TABLE 1

Cardio-renal record

Name.....Doctor.....Friend.....
 Address.....Address.....Address.....

Complaint:

F. H. Cardio-renal.....
 Nervous:.....

<i>P. H. Infections</i>	<i>Constitutional</i>	<i>Chem. Toxins</i>
Ever sickabad:.....Meas:.....	Convulsions.....	Alc:.....
Appx:.....Rblla:.....	Nervousness.....	Arsenic.....
Arth:.....Men:.....	Pituitary:.....	Gas:.....
Bron:.....Mps:.....	Protein xs:.....	Lead:.....
Colds:.....Pert:.....	Ptomain pois:.....	Salts xs:.....
Cpox:.....Pleu:.....	Rash:.....	
Diarr:.....Pneu:.....	Serum dis:.....	<i>Physical Trauma</i>
Diph:.....	Skin lesions	Inj:.....
Gallbl:.....Se. F:.....	Bad burns.....	Ops:.....
Hookwm:.....Tons:.....	Chr. ulcers:.....	Shock:.....
Influ:.....Typh:.....	Erysipelas:.....	Strain:.....
Mal:.....Ge:.....		Exposure:.....
Syph:.....		

Age:.....*Tea, ec. i. d.:*.....*Wt. max. str:*.....*Army ser. no:*.....
M. S. W.:.....*Cof., ec. i. d.:*.....and date:.....*Rank:*.....
Educ:.....*Alc:*.....*Wt. at enl.*.....*Co:*.....*Regt:*.....
Occup:.....*Tob. pipes:*.....and date:.....*Tagged:*.....
Habits:.....*Tob. cigts:*.....*Wt. now:*.....*Date seen:*.....
Bulimia:.....*Drugs:*.....*Traind mos:*.....
Meat:.....*BM:*.....*Trained at:*.....
Salt:.....*Exercise:*.....*Arrd France:*.....
Spices:.....*Sleep:*.....

P. I. Freq:.....*Stones:*.....*Cgh:*.....*Prec. pain:*.....
D...x...N...x... *Bldy urine:*.....*Spt:*.....*Arm pain:*.....
Since:.....*Ed. lids:*.....*Lum. ac:*.....*Blurring:*.....
D...x...N...x now: *Ed. feet:*.....*Hdac. since*.....*Anorexia:*.....
Urgency:.....*Dysp. since:*.....*Hdac. site:*.....*Naus:*.....
Incont:.....*Dysp. degree:*.....*Hdac. freq:*.....*Vom:*.....
Oliguria:.....*Palpit:*.....*Hdac. AM-PM:*.....*Jaund:*.....
Dysuria:.....*Dizzy:*.....*Hdac. degree:*.....
 Faintg:.....*Hdac. incr. by:*.....

TABLE 1—*Concluded*

<i>P. H. Infections</i>	<i>Constitutional</i>	<i>Chem. Toxins</i>
<i>P. E.</i> TPR:.....	Nose:.....	Lungs
Ht:.....	Wt:.....	Tongue protr:....
Theoret Wt:.....	tremor:.....	PN:.....
Bones:.....	coat:.....	Base rt:.....
Nutritn:.....	Teeth crowns:....	It:.....
Posture:.....	caries:.....	BS:.....
Facies:.....	fillings:.....	Rales:.....
Exag:.....	Gums leadline:..	Heart
Skull tend:.....	pyor:.....	size:.....
Skin:.....	Tons. enl:.....	thrills:.....
Anemia lids:.....	red:.....	arrhyth:.....
Cyan. lips.....	pus:.....	A ₂P ₂ :.....
Ed. lids:.....	tend:.....	murs:.....
Ed. feet:.....	Neck scars:.....	rate supine after
Eyes bulge:.....	glands:.....	40 bends:.....
Lag:.....	Nyst:....	stiff:.....
Converg:.....	Thyr. felt:.....	BP, S:.....
Conjunc:.....	tend:.....	D:.....
Pup:.....	Ax. glands:.....	murs:.....
Ears tophi:.....	Hands cyan:.....	
disch:.....	cold:.....	

been designed to include the various topics considered in **cardio-renal** studies by others. Current clinical and laboratory findings were recorded on forms like tables 2 and 18 (clinical table).

In presenting these data for discussion, brevity has been sought by omitting the protocols that could not concisely be consolidated in table 19 (summary of clinical notes). The individual clinical tables with the details of repeated tests have been reproduced in table 18 only for the more striking cases.

Technic. Microscopic sediments were done on all patients at least twice and on the average four times, generally weekly. The specimen was invariably the night urine, passed on rising and sent while fresh to the laboratory, where the examination was done by Dr. W. G. Webber; an appreciable advantage in view of the frequency of microscopic blood.

Phenolsulphonphthalein 1 cc., i.e., 6 mgm., was injected into the gluteal muscles, 200 cc. of water given to drink, and the urine collected at the end of two hours.

Blood pressure was tested with a Nicholson-Princo sphygmomanometer, i.e., mercury in U-tube and 15 cm. (6-inch) cuff, with the patient recumbent, with the auscultatory method, and regarding the appearance and disappearance of sound while the column was falling, as the systolic and diastolic tension respectively.

The two-hour test of renal function was carried through without any of the special diets used by those who invented the test (5) and by those who so greatly developed it into a practical clinical method (6, 7, 8). As it was impossible to quantitate nitrogen or even salt, advantage was taken of Mosenthal's

TABLE 2

Two-hour test. Case No. 3

DATE	PERIOD	OUTPUT	SPECIFIC GRAVITY	ALBUMIN
November 13-14		cc.		
	6 a.m.- 8 a.m.	115	1012	HT
	8 a.m.-10 a.m.	55	1020	T
	10 a.m.-noon	50	1015	HT
	noon- 2 p.m.	150	1010	HT
	2 p.m.- 4 p.m.	40	1007	HT
	4 p.m.- 6 p.m.	190	1010	HT
	6 p.m.- 8 p.m.	285	1010	HT
	8 p.m.- 6 a.m.	730	1008	HT
Total.....	1615	1007-20	T-HT

view that much may be learned even with a normal diet. The food furnished to these men was prepared with some restriction of protein, purins, and salt; and no salt was served. The approximate composition of what was served, on a day taken at random, was figured from food tables, with the following result which corresponds rather with the sparing-test-meal or low-diet (8).

Jam 80 grams, bread 280 grams, oatmeal (raw weight) 60 grams, mashed potatoes 500 grams, rice pudding 250 grams, milk 120 cc., butter 30 grams, cocoa 200 cc., soup 500 cc., sugar 70 cc. This yields about 64 grams protein, 58 grams fat, 450 grams carbohydrate, 8 grams salt, and 2600 calories. Fluids were

restricted only in the one decompensated case with anasarca, being generally about 1800 cc. About a third of the tests were done with the patient in bed, and all patients were tested after the edema had disappeared. The technic was carried out by the following orders:

1. The patient will read these directions, while the wardmaster will make such explanations as may be necessary, and see that the patient understands them, the night before beginning the test.

2. At the same time the wardmaster will give the patient a tin (carefully cleaned and boiled out with alkali), labeled: "Rising specimen."

3. In the morning at 6 a.m. the night orderly will see that the patient empties his bladder, will pour the specimen into a laboratory bottle, will mark it: "Rising urine—fresh specimen—for routine and micro." and see that it is taken to the central laboratory before 8 a.m.

4. On delivery of this tin, the patient will receive a can labeled: 6 a.m.—8 a.m.

5. Any urine passed during this period will be saved by the patient in this tin, and at the end of the period, within one minute of the hour, he will empty his bladder, and bring the whole amount immediately to the wardmaster. Before sitting down to a bowel movement the patient will always urinate in the tin, so that no urine whatever may be lost during the twenty-four hours that the test lasts.

6. No food or fluid of any kind, not even water, will be taken between meals, not even during the night; and breakfast must not be touched until the night specimen, 8 p.m.—6 a.m., has been completed.

7. On delivery of the specimen at the end of each period, the patient will get in exchange a tin properly marked for the next period.

8. On handing in each specimen, the patient will report to the wardmaster any accident that may have occurred, whether in eating, drinking, or collecting.

The collected specimens were taken promptly downstairs to the hospital dispensary, where the volume, specific gravity, and albumin were determined by, or under the supervision of, the sergeant in charge, a registered pharmacist, J. A. Ankenbrandt of Philadelphia. The form found convenient is seen in table 2.

ETIOLOGY

War or trench nephritis. The chief of a French hospital at the front for more than three and a half years has said: "These war nephritides are due to exactly the same causes as in peace" (9). A British writer (10) agrees that trench nephritis differs little from that met in civil practice. The present series also agrees, except for the addition of trench foot as a possible cause. In other words this series, being 30 per cent chronic and showing no uremic manifestations and only one case of general edema, hardly supports trench nephritis as a new entity.

Heredity. Small support can be extracted from this series. Two men gave a history of "kidney trouble" in 2 antecedents and 9 gave a history in 1 relative. For instance, "father has had kidney trouble for ten years, but is still alive." Even if such statements signify nephritis, it remains doubtful whether that nephritis transmitted any renal weakness, in view of the number of nephritics in the world with healthy descendants, so far as known. A series of controls on such descendants would be instructive, especially when the ancestral ailment appeared to be of the degenerative rather than the infectious type.

Evidence has been adduced that "a patient with a positive family history is a little more apt to develop a severe case. . . . Dividing the series roughly into two groups, graded as to severity, the first . . . marked . . . the second . . . showing few or no symptoms except the urinary findings," Vander Veer (11) found that among his twenty severe cases 35 per cent gave a history of probable kidney disease in the immediate family, vs. only 16 per cent of his twenty-five mild cases. This interesting suggestion is controverted if anything by the present series: 15 per cent of the twenty-six severe cases vs. 23 per cent of the thirty mild ones gave a family history.

Age. The age varied from 20 to 36, with an average of 26 years. If, instead of this arithmetical mean, we consider the mode, i.e., the most frequent age, we find 23 years; but this fashion is so slightly noticeable that it does not warrant depar-

ture from the usual rule of going by the mean. Seventy-nine per cent of the series were in their twenties, vs. 21 per cent in their thirties. The frequency-distribution follows:

Age.....	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Total
No. of cases	1	4	5	7	4	5	4	5	4	5	2	5	3	1	0	0	1	= 56

Civil occupation. A clue is sometimes obtainable to a trade toxin, chemical or physical, which the patient has not realized to be a possible factor, or has forgotten. Such are alcohol, arsenic, gas, lead, each of which will be discussed below. The occupation was sedentary, in general without exposure, in 33 per cent of these patients; and active, in general with exposure, in 67 per cent.

Arm of service. From this also a clue might be obtained, especially to gassing or weather exposure, "but to get some indication from these figures one would need to compare them with the number of effectives in each arm, which are not available" (10). Several writers have neglected this essential control.

Epidemiology. No two cases from any organization.

Acute infections. In 27 per cent of the series the onset was immediately preceded by an acute infectious disease. These 15 cases were: acute bronchitis 8 (including 5 influenzas, so-called, for there were no positive bloods or sputa), common colds 3, diphtheria 2, mumps 1, lobar pneumonia 1. In 32 other cases an acute infection was noted in the past history, but seemed more remote than the exposure which was also noted.

Chronic infections. Tuberculosis: "How often, in the absence of suspicious family history, past history, and physical examination . . . has closed latent parenchymatous tuberculosis of the kidney been misinterpreted as mild nephritis?" (12). I can not say for this series, since no sediments were stained for tubercle bacilli or inoculated into guinea-pigs; however loss of weight, continued fever, dysuria, costo-vertebral tenderness, and lung abnormalities were specially looked for and excluded.

Syphilis: "The ignorance of 95 per cent of doctors in dermatovenereology exceeds imagination. . . . It is truly scandalous

. . . . The responsibility may be traced to a fearful gap in our medical teaching" (13). None the less, the pale spirochete is so frequent that it has been frequently suspected as a cause of nephritis. "Towards the end of the primary stage and in the secondary stage, an albuminuria, syphilitic in origin, which may assume huge proportions with few or no casts, frequently occurs. These cases are due to the action of the toxin on the kidney, and in the early stage usually show only slight anatomical and functional changes" (14). A noted French writer has this to say: "Secondary syphilitic nephritis is revealed most frequently by sudden and considerable dropsy and by albuminuria which frequently reaches 15 grams daily. Tertiary lesions of syphilis are met relatively seldom in military practice" (15).

The present series supports those who have insisted that nervous syphilis is relatively frequent and also often relatively *early*, and by no means always a tertiary or late lesion (16, 17, 18). Of these 56 nephritics 7 per cent showed syphilis (nos. 3, 10, 26, 31), the last three with involvement of the central nervous system. Now "tabes is one of the nervous affections which provoke the most numerous and most varied urinary troubles. These may exist in all stages and may almost always be discovered in the pre-ataxic stage, sometimes without any other sign having attracted attention" (19). Of my 3 patients only 1 was notable for urinary troubles; these might be attributed to vesical nerve origin but other features gave evidence of associated nephritis. This was not the typical highly albuminous type mentioned above but was in keeping with the view: "Until recent years syphilis was accused of provoking principally the acute nephritides. . . . Recently under the stimulus of the work of Letulle and his pupils, of Debove, it has been asked: what is to prevent syphilis causing chronic nephritis?" (20).

Other spirochetes were unfortunately not looked for in the urine, in view of the spirochetel nephritis reported (21); and especially in view of the latter writer's note of the frequency with which the only sign is hematuria (often microscopic only), and in view of the frequency of hematuria in otherwise mild cases of this series.

Focal infections: Chronic arthritis was thought responsible in only 1 case, though it was present in 11 cases. Repeated common colds were incriminated in 3 cases. Cholecystitis in none. Otitis media in 1, though present in 3. Repeated tonsillitis in 2. Prostatitis in none. Furunculosis (22) in none.

Constitutional causes. The following were considered but not found: convulsions, deficiency diseases, diabetes mellitus, neuroses, pituitary (no acromegaly, choked disk, dystrophia adiposogenitalis, persistent headache, extreme polyuria; visual fields not tested), posture, protein excess, ptomain poisoning, rash, serum disease, skin destruction such as burns, eczema or ulcers.

Simulation or true malingering is "in general very rare, whereas exaggeration is extremely frequent," since the former "requires a consummate knowledge to have any chance of success, whereas the latter is as easy for the subject to maintain as it is arduous for the physician to diagnose and difficult to demonstrate" (23). Simulation has been reported (24) of incontinence, polyuria, albuminuria (by addition, substitution, or even injection into bladder), hematuria, pyuria and traumatic nephritis. In the present series feigning was hardly to be expected as the armistice was signed and the men were already hospitalized before the nephritis was noticed; in fact it was found in no case. A tendency to exaggeration was noted in two men as moderate, in four as mild, but all 6 had plain objective signs.

Chemical toxins. Alcohol was not conspicuous. Arsenic "provokes edema of the face, especially the eyelids" (25), presumably an early symptom of metal poisoning of the kidney. No history of this drug was obtained. Gassing was reported by thirteen patients but did not seem responsible. Plumbism: Occurring in a quantity of trades other than painting, lead is however often overlooked, and therefore in them may be more dangerous though handled in smaller amounts. In this series it was unimportant, having been handled by only two men; both had always washed their hands carefully, and had no colic, headache, leadline, anemia, palsies or abnormal reflexes; no. 18 showed hypertension but also another good cause for the nephritis, i.e., chronic otitis media; while no. 53 showed no hypertension and

seemed a nephritis from exposure. Salt and other habits supposed to damage kidney function are recorded in table 3. Although their significance cannot be defined in the absence of controls on individuals demonstrated free from renal disease, the striking fact is that salt consumption "in larger amounts than the average," with or without other excess, was present in the large number of 27 patients, i.e., 48 per cent. An even higher figure has been reported (11): 60 per cent, vs. only 26 per cent in non-nephritic controls.

Physical trauma, acute or chronic. No evidence pointed to injury, operation, shock or strain; but much incriminated weather exposure. Cold appears to some to play only a secondary part

TABLE 3

Habits

Normal.....	24
Coffee, in excess.....	3
Meat, in excess.....	1
Alcohol, in excess.....	1
Coffee and salt (and spices), in excess.....	1
Alcohol and salt, in excess.....	1
Alcohol and salt and meat, in excess.....	1
Salt and meat, in excess.....	10
Salt.....	14
<hr/>	
Total.....	56

(10) and it must be granted that in many cases the causation is open to question. In general however "exposure to cold and wet is one of the most common causes of acute nephritis" (26), and during the war in particular its influence has been emphasized again (27), most clearly in the following case (28):

A sailor, age twenty-six, in full health, was torpedoed and was in the water for several hours in winter. He presented abruptly anasarca, lumbar ache, dyspnea, fever of 102°F., "râles of pulmonary congestion," but heart free from enlargement and murmurs; blood pressure 170-50, oliguria of 200 cc., massive albuminuria of 61 grams in twenty-four hours, granular casts, red cells, chloride retention, nitrogen retention, i.e., 101 mgm. urea per 100 cc. blood, vision and fundi normal, Bordet-Wassermann negative. Past history revealed no syphilis, tuberculosis,

malaria, old or recent infectious diseases. On discharge, eleven months after admission, the edema had gone with a loss of 18 kgm., the twenty-four hour amount was 3000 cc., no albumin, blood urea 40 mgm., the "methylene blue test of renal permeability satisfactory."

Exposure prior to enlistment was present in 38 cases, i.e., 67 per cent. This percentage seems to declare an outdoor worker more prone to nephritis than an indoor one. While this may be true in general, analysis of these 38 patients just mentioned indicates that their exposure in civil life was responsible in at most 2 (nos. 1 and 43).

TABLE 4

Etiology

Alcohol.....	0	Mumps.....	0
Arthritis, chronic.....	1	Otitis media, chronic.....	1
Bronchitis acute.....	3	Pneumonia, lobar.....	1
Common colds, chronic.....	3	Salt excess.....	0
Diabetes.....	0	Simulation.....	0
Diphtheria.....	2	Syphilis.....	0
Exposure with acute diarrhea..	25	Spirochetal.....	0
Exposure alone.....	7	Tonsillitis, chronic.....	2
	—	Trench foot.....	5
Exposure, total.....	32	Tuberculosis.....	0
Gassing.....	0		—
Heredity.....	0	Total.....	56
Influenza.....	5		
Lead.....	0		

Exposure in the trenches or behind the lines was reported by 51 patients, i.e., 91 per cent. This apparent frequency again, as with civil exposure, is not as bad as it seems; for as good if not better causes were traced in all but 32 cases, i.e., 57 per cent attributable to exposure. The duration of this war exposure has varied from eleven months down to one day. The latter seems short indeed to be responsible but is less surprising than the case of the sailor cited above.

Trench foot. This condition as well as trench fever is said to have been seen accompanied by acute hemorrhagic kidneys post mortem. Whether the cause is bacteriological or physical (cold with pressure), both features preceded the five cases, i.e., 9 per cent of the series, giving a history of trench foot. Four still

showed on reaching this base swelling, redness and tenderness, usually metatarsalgia in type. In these five men therefore the trench foot and the nephritis have been considered cause and effect, though it seems more likely that they are both effects of a common cause as yet unknown.

SYMPTOMS, SUBJECTIVE

Initial symptom and symptom sequence. The lure of earlier diagnosis has long led to the hunt for pathognomonic features, whether subjective symptoms or objective signs. The authoritative affirmation for example was recently made: "The frequency of lumbar pain, dull and aching in character, as one of the first symptoms . . . is striking and has not we believe been sufficiently emphasized" (3). All it suggests to many a doctor (even a recent graduate from an A-1 medical school, though he however examines the urine for security) is to urge on the patient that he has no kidney trouble but only anxiety from reading quack pill advertisements.

Other indicator symptoms also have not I believe been sufficiently emphasized. This belief has been in mind constantly and now is evidenced by the following procedure. The symptoms were numbered in the order in which they seem to have been noticed in each case, then the number of times each symptom was "1" was counted and the symptoms numbered in the order of their frequency as the first symptom. Results: in the 30 relatively advanced cases cited (3), this sequence appears to have been: Edema of feet, headache, dyspnea, lumbar ache, blurring, nycturia. On the other hand, in the present 56 newly diagnosed, relatively incipient cases, the first symptom was most often: Nycturia; then dyspnea; then (tie) edema of lids, edema of feet, and lumbar ache; then headache. The second symptom in order of frequency was: Nycturia, edema of lids, dyspnea, edema of feet, then (tie) lumbar ache and headache. To make this clearer, these last two lists were consolidated, giving the symptoms in order of frequency of occurrence in either first or second place as: (1) Nycturia, (2) edema of lids, (3) dyspnea, (4) edema of

feet, (5) lumbar ache, (6) headache. Great importance is attributed to this list. For while it must be admitted that they were all absent in 9 per cent of this series (nos. 14, 31, 35, 48, 53), other nephritic features occurred with so much less regularity that it is insisted that earlier diagnosis depends on vigilance for these six suggestive symptoms.

Constancy of symptoms. Further demonstration of the steadiness of these six compared with the irregularity of others is seen in table 5.

TABLE 5
Percentage of cases in which each symptom was present

BROWN'S SERIES (29)	ROBINSON'S SERIES (31)	THIS SERIES
<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Edema..... 91	Edema..... 98	Nycturia..... 84
Dyspnea..... 85	Dyspnea..... 94	Edema, lids..... 52
Lumbar ache..... 64	Weakness..... 88	Dyspnea..... 43
Frequent micturition.. 14	Lumbar ache..... 80	Edema, feet..... 37
	Headache..... 74	Lumbar ache..... 23
	Leg ache..... 64	Headache..... 23
	Vertigo..... 62	Bronchitis..... 21
	Tracheobronchitis... 54	Painful micturition... 11
	Vomiting..... 52	Vertigo..... 9
	Chills..... 50	Blurring..... 9
	Nycturia..... 40	Cough..... 0
	Sore throat..... 34	Vomiting..... 0
	Belly pain..... 32	Coryza..... 0
	Joint pain..... 30	Leg ache..... 0
	Fever..... 24	Chills..... 0
		Sore throat..... 0
		Belly pain..... 0
		Joint pain..... 0
		Fever..... 0

Nycturia. Nocturnal pollakiuria, Night frequency: It has been affirmed that "any necessity of breaking one's sleep . . . is pathologic, except when an abnormal amount of fluid has been taken before retiring" (32). Other undoubted exceptions are: coffee, vichy or similar alkaline waters, and alcohol. The last exception may be picturesque: "It is not rare to see polyuria begin suddenly after several days of Homeric libations" (19). Alcohol in moderation of an evening may on the contrary stop a nycturia which has otherwise caused the individual to get

up at 5 o'clock every morning. This curiosity has been noticed previously in two cases, both apparently otherwise normal, both as to physical examination and as to neuroses—not "faux urinaires" (33). The protocol of one of them follows:

E. S., physician, age thirty-two; measles and scarlatina in childhood, both mildly, and no severe sickness since. He reported getting up once to twice at night as long as ten years ago but was assured by his doctor that his urine was normal. The nycturia has been almost invariable, the usual exception being after dining out, about four to eight times a month. Annually for the last three years the gamut of tests has been normal: albumin, sugar, microscopic, 2-hour, blood pressure, and phenolsulphonphthalein. The only explanation seems to be his habit from childhood of drinking two to three quarts of water, lemonade, or weak tea. This habit naturally produced frequency, which has persisted at night though not in the daytime since the fluid intake has been cut below 2 liters for the past three years.

In view of such cases, many may doubt the significance of Kahn's statement, but the great importance of inquiry into nycturia is supported by the evidence below.

So-called bladder weakness, vesical weakness, or latent enuresis, meaning thereby increased frequency of micturition, is extremely common among soldiers (34). In one report on this subject great stress was laid on hereditary disposition and on the frequency with which mental defects and stigmata of degeneration were present in the patients (35). In this series no instance of pollakiuria was attributable to such neuroses.

Nycturia was vastly the most common presenting symptom and also the least commonly explicable otherwise than by nephritis, hence it was the most valuable index to this disease. In these 56 patients it was attributed to extra-renal etiology in no case, although it did lead to confusion in some patients who showed no other renal feature and who were therefore dropped; in them it was ascribed to the large amount of coffee and vichy water drunk. It was the only symptom in 14 per cent (nos. 1, 4, 26, 30, 38, 42, 46, 47); and the only symptom but one in 21 per cent of the series, and besides in these last it remained the main symptom since the accompanying symptom could in

11 out of the 12 cases be assigned to extrarenal factors, as shown in table 6. On the other hand it was absent in 9 cases, i.e., 16 per cent. In 5 of these no symptoms whatever were present and in the other 4 cases where it failed there was palpebral edema, with or without another symptom.

No. 9.....	(1) Headache,	(2) Lid edema
No. 20.....	(1) Dyspnea,	(2) Headache, (3) Lid edema
No. 41.....	(1) Dyspnea,	(2) Lid edema
No. 54.....	(1) Dyspnea,	(2) Lid edema

Nycturia occurred as the initial symptom in 28 cases, symptom (2) in 13 cases, (3) in 4 cases, (4) in 2 cases, and absent in 9 cases. Of these 9, 5 had none of the index symptoms (nos. 14, 31, 35, 48, 53).

TABLE 6

Nycturia with only one other symptom

No. 2....	Edema feet, which was symp. (2); assignable to arthritis.
No. 6....	Lumbar ache, (1); influenza.
No. 21....	Dyspnea, (1); influenza.
No. 22....	Edema, feet, (1); trench foot.
No. 24....	Edema, feet, (2); trench foot.
No. 28....	Edema, feet, (1); trench foot.
No. 32....	Dyspnea, (2); chr. tonsils.
No. 33....	Headache, (1); trade accounting.
No. 34....	Edema, lids, (1); "always the same."
No. 37....	Dyspnea, (2); Nephritic heart.
No. 44....	Headache, (2); very rare: unimp?
No. 55....	Edema, lids, (1); "always the same."

When nycturia was a symptom, the physical signs present were: albumin in 85 per cent, casts in 64 per cent, microscopic blood in 51 per cent, hypertension in 42 per cent, night specific gravity 1.017 or less in 17 per cent, range of specific gravity eight points or less in 15 per cent, highest specific gravity 1.017 or less in 6 per cent.

The importance of inquiry for nycturia, as routine on all cases, so that early nephritics may be recognized and safeguarded, needs emphasis. Many patients, while aware that their nycturia is abnormal, make no complaint. Perhaps this is due to the fact that the nocturnal pollakiuria is after all in some cases not so very frequent, i.e., three times or less in 68 per cent of this series:

Frequency.....	0	1×	2×	3×	4×	5×	6×	7×	8×	9×	10×	11×	12×	
Number of cases..	10	4	14	10	5	8	3	0	1	0	0	0	1	= 56

Diurnal pollakiuria. The normal day frequency seems to be five times, i.e., on rising, with the "after-breakfast defecation" (36), before noon meal, before evening meal, and before bed; though with many exceptions due to extra drinks, cold weather, apprehension, and the like. This estimate of normal was exceeded by 34 per cent.

Frequency.....	2×	3×	4×	5×	6×	8×	10×	15×	
Number of cases.....	3	7	13	14	8	4	4	3	= 56

Total twenty-four hour frequency. This exceeded five times in 71 per cent.

Frequency:

2×	3×	4×	5×	6×	7×	8×	9×	10×	11×	12×	14×	16×	20×	21×	27×	
2	1	2	11	10	4	3	3	5	6	2	3	1	1	1	1	= 56

Urgency. In 14 per cent of the patients (nos. 2, 5, 43, 44, 46, 49, 50, 56), significance not clear.

Incontinence. Enuresis with normal urines has, like the above mentioned latent enuresis or bladder weakness, been reported as frequent in soldiers (37,); similarly also it generally existed prior to entry into service. Enuresis alone was present in 1 patient (no. 51), while it was present with day incontinence as well in 3 patients (nos. 5, 10, 49), total 4 cases, i.e., 7 per cent of the series. Central nervous syphilis was found only in no. 10; in the other 3 no epilepsy was traceable, or other explanation.

Dysuria. Pain on micturition was reported by 11 per cent of the patients (nos. 4, 5, 10, 11, 16, 56). In all 6 cases the pain was rare, history of stone and gonorrhea was negative, no urethral discharge was found and the smear after prostatic massage was negative.

Calculus. History suggestive of stone was given by one case, no. 45; one attack in the summer of 1914 of indefinitely localized ureter or vesical pain; an instrument was passed and on the next day some blood was seen; since then no pain, retention or blood.

Smoky urine. Gross hematuria was seen in only 1 patient, no. 8. On admission the blood was microscopic only. After four days, when the decompensation began to improve, a phenol-sulphonphthalein test was thought safe; however within four hours the urine turned mahogany color. This continued for four days; two days later a sediment showed fewer red blood cells than on admission. Cases with microscopic blood will be discussed below among other physical signs. The danger of using drugs in the acute stage has been discussed by others (38).

Edema of the lids. This is the most constant symptom of all. It was the commonest symptom both in Dyke's and Robinson's series (90 per cent and 98 per cent), and the second commonest in this group (52 per cent). When it was absent in this series, all other symptoms were also absent in a third of the cases. It was explicable otherwise than by nephritis in only 7 per cent of the cases in which it occurred; i.e., two patients, who stated that their puffy lids had been always so, but this explanation is not necessarily extra-renal since both of them (nos. 34 and 55) had hypertension and may have had their nephritis so long that they had become accustomed to the swelling in the face. It was the only symptom but one in 9 per cent of the series (nos. 9, 34, 41, 54, 55). It was the initial symptom in 6 cases, i.e., 11 per cent versus 22 per cent in Dyke's series; it was symptom (2) in 11 cases, (3) in 5 cases, (4) in 3 cases, (5) in 2 cases, (6) in 2 cases, and absent in 27 cases. It seems worth repeating that, in the 4 cases showing no nycturia but showing one or two other symptoms edema of the lids was the only symptom present in all 4 cases; in other words any patient free from nycturia and lid edema seems in the highest degree unlikely to show nephritis; 84 per cent of this series had either nycturia or lid edema, 16 per cent had no symptom whatever. The duration of the edema was not adequately recorded to study the recent dictum that its persistence after the second week renders the prognosis increasingly unfavorable (10, 38, 39). Only the date of its occurrence prior to admission was noted, and not its duration, which was in most cases transient. This data is seen in table 7.

Dyspnea. This was the second most constant symptom in Robinson's series, occurring in 94 per cent; and third most constant in Dyke's and the present series, i.e., 47 per cent and 43 per cent. As presenting symptom it took third place in the present group, after nycturia and edema of lids. It was the only symptom but one in 5 cases, and in these the other symptom was either nycturia or edema. Extra-renal etiology seemed present in 4 out of the 24 men who admitted some breathlessness, namely gassing. Severity was notable in only no. 8; the other 23 did not complain but simply admitted the symptom when questioned.

TABLE 7
Time of appearance of lid edema

TIME BEFORE ADMISSION	CASES	NUMBER OF CASES
1 day	Nos. 9, 10, 15, 23, 27, 36, 41, 43, 54	9
2 days	Nos. 3, 20	2
3 days	No. 12	1
6 days	No. 13	1
1 week	Nos. 5, 17	2
2 weeks	No. 11	1
3 weeks	Nos. 8, 51	2
1 month	Nos. 7, 29, 49, 50	4
4 months	No. 40	1
9 months	No. 52	1
3 years	Nos. 9, 18, 56	3
"Always"	Nos. 34, 55	2
Total.....	29

Palpitation. In 17 per cent of the patients (nos. 2, 15, 19, 37, 43) who had dyspnea; mild and inconstant in all.

Precordial pain. In none.

Vertigo. In only one of the men with dyspnea, no. 18, and he had chronic otitis media to account for it. Also present in 4 men without dyspnea (nos. 2, 9, 26, 33) or other explanation.

Sensitiveness to cold. In 3 patients with dyspnea (nos. 15, 16, 43), and in 2 without (nos. 9, 10).

Cough. In none.

Lumbar ache. Lumbago or pain in the kidneys, without local tenderness or pyuria, occurred in 23 per cent of the series.

Headache. Also present in 23 per cent. No skull tenderness or significant eye-ground changes were detected by the ophthalmologist. Refraction was not tested. A statement of blurring was elicited in 5 cases but was too vague to be called amblyopia.

Vomiting and jaundice. Absent.

OBJECTIVE SIGNS ON PHYSICAL EXAMINATION

Constancy of signs. Albumin in 86 per cent, casts in 64 per cent, microscopic blood in 50 per cent, hypertension in 41 per cent, and low phenolsulphonphthalein output in only 5 per cent. Abnormalities in two-hour test were varied: Night volume reached 401 cc. or more in 50 per cent, 751 cc. or more in 25 per cent, night gravity was 1.017 or less in 20 per cent, range of variation was fixed to eight or less in 16 per cent, and highest gravity was 1.017 or less in 5 per cent of the cases. Estimating the constancy of these deficiencies in the 255 tests, instead of in the 56 cases, we get: Night gravity low in 45 per cent, fixation in 32 per cent, night amount 401 cc. or more in 31 per cent, maximal gravity low in 13 per cent, night amount 751 cc. or more in 11 per cent. A higher percentage of abnormalities would have been detected if I had been aware of the merit of the stimulating-test-meal or high diet (8).

Fever. No. 16 had 99.4°F., with slight sore throat, but no redness, for three days.

Rapid respiration. Absent.

Anemia. Hemoglobin was tested by Tallqvist on all patients. No. 50 had 65 per cent, but his red blood cells were 4,300,000.

Goiter. Among men of draft age "a remarkable number of thyroid enlargements was noted, . . . many unmistakably toxic; . . . and the more toxic cases show a tendency to nephritis" (40). The percentage of goiters to show toxic signs was, as nearly as I can judge from their figures, more than 50 per cent; in another recent report it was 11 per cent (41): while in this series it was, as would be expected in men accepted for the army, nil. In other words the following signs were watched for in vain.

Eye signs: Exophthalmos, wide fissure (Dalrymple-Cooper-Swanzy), imperfect or diminished frequency of winking (Stellwag), lid lag (von Graefe), weak convergence (Moebius) (42).

Fine tremor: of hands or tongue.

Tachycardia. Only 6 per cent of Smith's toxic cases had a pulse, recumbent, before exercise, below 100. In this series, the nine goiters all had a resting pulse of 90 or less.

TABLE 8
Summary of signs in the 24 cases with dyspnea

	NUMBER OF CASES	PER CENT
Edema of feet.....	21	87
Cardiac enlargement, of 1 cm., by palpation or percussion....	14	58
Hypertension.....	14	58
Exercise tolerance weak*.....	11	46
Defective circulation in extremities.....	16	28
Hands cyanotic.....	1	
Hands cold to touch.....	3	
Hands cyanotic and cold.....	2	
Feet cyanotic.....	0	
Feet cold.....	3	
Feet cyanotic and cold.....	0	
Hands and feet cyanotic.....	1	
Hands and feet cyanotic and cold.....	6	
Cyanosis of lips.....	0	
Thyrotoxicosis.....	0	
Precordial tenderness.....	0	
Persistent tachycardia; not studied.....	0	
Thrills or murmurs.....	0	
Arrhythmia.....	0	

* Interpreted as a pulse above 80 recumbent, two minutes after having "exercised bending forward and touching the floor rapidly forty times, used because noiseless and vigorous" (44).

Tenderness, to palpation or pin-point, as a sign of incipient goiter (43).

Simple goiter then was present in this series in 9 cases, i.e., 16 per cent. Of these, 3 had no dyspnea (nos. 4, 9, 48) while it was present in 6 (nos. 12, 18, 19, 20, 25, 54).

Circulation. No diagnosis of acute or chronic cardiac valvular disease was made. The physical signs in the patients admitting dyspnea are schematized in table 8.

Hypertension. Definition: Systolic 140 or more, or diastolic 90 or more; provided the average of all the systolic pressures noted on the patient did not fall below 135 and the diastolic below 85. The constancy of this symptom was 41 per cent of the series. Of these 23 hypertensives, the nephritis was thought acute in 43 per cent (nos. 3, 7, 12, 20, 25, 34, 48, 49, 54, 56), and chronic in 57 per cent (nos. 2, 5, 8, 16, 32, 36, 37, 38, 40, 43, 46, 51, 55). It is surprising to find high pressure associated with so many apparently acute nephritides; possibly they should be called low-grade chronic and correspond to this statement: "Perhaps the majority of the cases in which the pathologist at autopsy writes down 'slight chronic nephritis' are only instances of obsolete scars whose cause it is now impossible to tell" (45). None the less the current idea that high pressure points toward chronic rather than acute disease, is supported by its presence in 76 per cent of the cases diagnosed chronic nephritis versus only 26 per cent of the cases thought acute. In 61 per cent of the hypersensitives *dyspnea* was present, but was slight in all, conversely 58 per cent of the patients with dyspnea had hypertension. Phenolsulphonphthalein: the freedom of these hypertensives from diminished dye excretion was notable, only 6 per cent of them showing a reading less than 50 per cent in 2 hours.

Diastolic versus systolic pressure: "The first fact furnished by the sphygmomanometer is a rise of the diastolic tension, while the systolic is unchanged or falls. . . . The indications of the diastolic pressure offer considerable value in prognosis. Thus its rise is more important than a rise in the systolic; it is the index of a serious state and permits recognition of the menace to the patient" (46). From this series no clear-cut support can be given to the above view. The diastolic tension was high, i.e., 90 mm. or more, in 46 per cent of the 56 patients. This figure compared with systolic hypertension in 41 per cent, can hardly be thought sufficiently higher to give effective support, though it would be if the series had been ten times as large.

If the definition given above strike the reader as too low, attention may be drawn to an even lower standard: "whereas in general . . . a pressure of 130 was regarded as patho-

logical, now 120 must be considered as probably elevated, and 125 as surely so" (47). Whatever criterion be preferred, the number of cases above that level may easily be read from table 9. In this tabulation of the frequency-distribution, the 3 different blood pressures, each at 4 different times in each patient's hospital stay, are consolidated by half, i.e., shown by 10 mm.

TABLE 9
Blood Pressure

mm. Hg	SYSTOLIC				DIASTOLIC				PULSE PRESSURE			
	Admission	Maximum	Minimum	Discharge	Admission	Maximum	Minimum	Discharge	Admission	Maximum	Minimum	Discharge
190.....	1	1										
180.....	2	2										
170.....	1	2		1								
160.....	3	4	1	3								
150.....	7	9	3	8								
140.....	13	13	8	8								
130.....	11	13	4	12								
120.....	14	10	22	18	1	1						
110.....	4	2	15	6		1						
100.....			2		5	6	1	2	1	1		
90.....			1		11	18	5	14		1		
80.....					21	21	10	18	6	8		2
70.....					10	7	18	18	4	10	2	5
60.....					6	2	16	3	13	14	7	13
50.....					1		5	1	16	14	14	17
40.....									10	8	20	15
30.....					1		1		6		13	4
Total cases.....	56	56	56	56	56	56	56	56	56	56	56	56
Average pressure.	138	141	125	135	82	87	71	80	56	65	46	54

instead of by 5 mm. as originally recorded; e.g., pressures of 125 are added in with those of 120.

The average value at the foot of each column is the arithmetical mean of 56 readings, one from each patient. This bottom row suggests support of the observation: "when we compare the blood pressure on admission with the maximum during hospital stay . . . frequently the highest values do *not*

occur on the day of admission" (48). And in fact the original readings prove that this rise after admission, instead of the expected fall, occurred in the 39 per cent of the cases, judging by systolic pressure; in 38 per cent by diastolic and in 57 per cent of the pulse pressures. No explanation is offered. A second suggestion from the row of averages is that, when we compare the value on discharge with the minimum during hospital stay, the lowest value does *not* occur at the time of discharge. And in fact review of the original figures shows that this unexpected rise toward the time of discharge occurred in 62 per cent of the systolic pressures, 59 per cent of the diastolic, or 66 per cent judging by pulse pressure, which would average 63 per cent for the three. The explanation may well be that, in about two-thirds of all cases, as the patient becomes more active preparatory to discharge, his pressure rises somewhat. This discharge pressure then represents, rather than the admission, maximal or minimal pressure so frequently quoted, the basal condition which can be hoped for in the patient's daily life, if safeguarded. Of the four values therefore it seems the most important.

Essential hypertension. If it should be granted that some of these hypertensives had no nephritis, the question would arise as to how many may have been "essential;" at most two cases in the 23, i.e., 9 per cent. No. 34 had a very slight trace of albumin once in 6 tests and a low night gravity twice in 6 tests. No. 56 had a slight trace twice in 9 tests.

Hypo-tension. This was noted in 1 patient only; no. 14 had no nycturia, edema, or other renal symptoms; signs were a trace of albumin on three successive days and a few red blood cells once. From the point of view of adrenal deficit, he showed: lax posture, downcast eyes, lassitude, dermatographia (white line of Sergeant, meaning a white instead of the usual pink line where the back of the thumb-nail had been rubbed across the chest (1, 49); blood pressure: highest 115-75, lowest 90-55; average of reading on six days 105-65. The hemoglobin was 75 per cent, the phenolsulphonphthalein 60 per cent. From the view-point of adrenal tuberculosis, he showed: flat chest and bronchovesicular breathing, but no râles before or after coughing, no temperature, no pigmentation; x-ray not taken.

Albumin. In the absence of both casts and blood, albumin has by some been considered insignificant, especially when intermittent, the variety of euphonious names used is given further on in discussing the type of nephritis. These more or less physiological factors are thought to have been excluded in the present series, by the rising specimen, two-hour, and other tests. The egg white provocative test (50) has not been used. Albuminuria was present in 47 cases, i.e., 84 per cent. It was accompanied by neither casts nor red cells in 9 cases, i.e., 16 per cent of the whole series, or 19 per cent of the albuminurias. Following the more cautious doctrine that "practically in all cases the presence of albumin indicates a change of some sort in the glomeruli, the nature, extent, and gravity of which it is difficult to estimate" (26), search was made for further evidence of nephritis, and not in vain. Albumin was absent in 9 cases, i.e., 16 per cent; of these two had casts (nos. 30, 54), 2 had blood (nos. 21, 42), 3 had both casts and blood (nos. 25, 31, 43), and 2 had neither casts nor blood (nos. 23, 27). Albumin was absent even more frequently, if we consider urines instead of cases; namely in 45 per cent of 530 specimens examined. The various topics figured above show the utter unreliability of excluding nephritis on a single examination negative for albumin, casts or blood; yet how frequently is the disease thus overlooked, and not only when incipient! The most striking example was one of the men with sub-normal phenolsulphonphthalein excretion: No. 41 reported no nycturia, had such slight lid edema that he had not noticed it himself, had very mild dyspnea, only a slight trace of albumin on two out of twelve days tested, no casts or blood in five sediments; but a low phenolsulphonphthalein test of 35 per cent, a night gravity of 1.013 twice and 1.015 three times, even with a night volume of no more than 330 cc. and as little as 90 cc. The same absence of albumin even with a phenolsulphonphthalein less than 50 per cent may be seen in acute nephropathy (51).

Casts. Present in 64 per cent of all patients, or in 66 per cent of those with albumin, or in 56 per cent of the nine without albumin, or in 50 per cent of the four cases with neither albumin nor blood. These facts support the opinion in the last para-

graph, that nephritis cannot be denied until after functional testing.

Hematuria. "Blood in the urine is always a serious matter, whether there are only a few red cells detected by the microscope or whether there has been profuse hemorrhage" (52). Gross blood was seen in only 1 patient, described above under symptoms. Microscopic red blood cells were detected in 50 per cent of all patients, or in 56 per cent of the 9 without albumin, or in 50 per cent of the 4 patients with neither albumin nor casts. When found, it was always seriously considered, but only half the time was it considered to be associated with serious symptoms or signs. In the other half it was interpreted as a

TABLE 10
Persistence of microscopic red blood cells
(Tests generally made weekly)

Red blood cells found once in.....	17 patients
twice.....	7
3 times.....	0
4 times.....	1 (No. 5)
5 times.....	3 (Nos. 12, 20, 51)
6 times.....	0
7 times.....	1 (No. 8)
8 times.....	1 (No. 3)
Total.....	30

real sign of nephritis, and not as "Gull's renal epistaxis, a disease of middle adult life marked by renal hemorrhage, but with no known lesion; called also essential renal hematuria, angioneurotic hematuria, renal hemophilia" (53).

"Slight leakage, represented by the constant presence of a few red cells, may be present early in the disease and persist for years" (54). In a recent report on 400 war nephritics, red cells were found in 90 per cent, and persisted as long as six months (55). In this series too obstinacy has been rather striking, having lasted more than a month in 6 patients, i.e., 20 per cent of the hematurias, and more than two months in 1 (no. 3). How much longer these 6 nephrorrhagias continued can not be told, as they were sent to the United States at the end of the times

specified. No case gave a history of bleeding from mouth, lungs or gastrointestinal tract.

Hemoglobinuria, hemophiliac tendencies, purpura. Absent.

Pyuria. Gross pus was absent. Microscopic leucocytes were present in 44 cases, i.e., 79 per cent of the whole series. In this group with a few white blood cells, the following features seemed worthy of note: pollakiuria present in 86 per cent of the group, red cells in 43 per cent, history of gonorrhea in 18 per cent but all 8 patients were negative for urethral discharge and also for gonococci in prostatic secretion expressed by massage; dysuria in 7 per cent, i.e., only 3 cases. The possibility of cystitis also seemed excluded by the extreme mildness of the dysuria and by the absence of bladder tenderness.

Glycosuria. Found in none. No. 52 gave a history of sugar eleven years ago, in bed for seven months; since then no diet, no loss of weight, nor urine tests till admission.

The two-hour test. This test of renal function, by study of the fractioned twenty-four-hour amount, has been very helpful in this series. For, although here not applicable in the detail developed by Mosenthal and by Christian, it has been done repeatedly: 297 times in all, averaging five times per case. "Extra-renal factors" which can distort the test have recently been well emphasized (56): dependence on a single test, varying water reserve of the tissues, varying temperature, chilling of the body surface, varying humidity, varying air circulation, varying metabolism, preferential and significant demand on body fluids by skin and lungs and lack of strict control of the test meal. And from these considerations it was concluded that "early diagnosis is hazardous and requires judgment with reservation." Reservation is no doubt prudent for the reputation, but if we hedge until the diagnosis is patent, our patient may well complain that "we arrived too late with all our science; diagnosis should have been made earlier" (57). Furthermore, "many cases of chronic nephritis are latent and are not recognized until the occurrence of one of the serious or fatal complications. Even an advanced grade of contracted kidney may be compatible with great mental and bodily activity" (54). Illustrations of this last sentence

were seen in 4 very typical (nos. 5, 12, 46, 55; having been going on for 18, 6, 6, and 3 months respectively), and six fairly typical cases (nos. 32, 36, 38, 39, 40, 44). These ten patients all "felt fine;" they amounted to as much as 59 per cent of the nephritides that were chronic. These things being so, surely the physician should hazard earlier diagnosis, or at least specifically prescribe care against chilling, against common colds and sore throat, against excessive meat and salt; for a patient in the incipient and therefore often doubtful stage, rather than with reassurances delay until the disease is certain and therefore often advanced and hopeless. The problem in practice of this attitude toward nephritis is the same as in the early diagnosis of heart disease, tuberculosis, or diabetes; the risk of being thought an alarmist. But must one not face the situation, avoiding the creation of a phobia in certain cases by applying the advice as to judicious precautions through a relative?

"Strict control of the dietary of the test meal" (56) has been insisted on most vigorously by others than those who have been instrumental in developing the test (5, 6, 7, 8). While constant conditions of observation are undoubtedly desirable, an arbitrary diet may suffer the defect of its virtue, to the extent that it varies from the patient's customary food. These two authors themselves, in discussing abnormal two-hour results which they found in a normal person with strict diet, admit the explanation that "the volume of fluid ingested may have been too low for the subject or the solid intake too high." On the other hand, for the patient to eat as usual may prove to be not only simpler but more scientific; especially if the intake be known, at least as "high, normal, or low," and considered in the interpretation of the results. That "instinct saves man . . . from the dangers involved in a too restricted choice . . . and is a safe guide . . . prompting us to eat the food we should," has lately received, to the bewilderment and annoyance of some, the authority of a profound contributor to the chemistry of metabolism (58).

Normal standard. Mosenthal's simple previous standard he now amends as regards the "night urine of 400 cc. or less with

a specific gravity of 1.018 or over." He concludes that "the height of the maximum specific gravity and the volume of the night urine are the most constant features of the normal test, regardless of the diet." The relative constancy of the various features in 124 tests on normal persons, analyzed in his table 5 is calculated here in table 11.

TABLE 11
Constancy of various features in normals

	<i>per cent</i>
Night volume 750 cc. or less in.....	100
Maximum specific gravity 1018 or more in.....	99
Variation of specific gravity 9 or more in.....	86
Night specific gravity 1018 or more in.....	73
Night volume 400 cc. or less in.....	70

The constancy of the various criteria in 255 2-hour tests on the fifty-six nephritics of this series is similarly shown in table 12.

TABLE 12
Constancy of various features in 255 two-hour tests in nephritics

	<i>per cent</i>
Night specific gravity 1017 or less in.....	45
Variation of specific gravity 8 or less in.....	32
Night volume 401 cc. or more in.....	31
Maximum specific gravity 1017 or less in.....	13
Night volume 751 cc. or more in.....	11

In table 13 is shown the constancy of the same abnormalities in terms of the 56 patients instead of in terms of all the 255 tests. For each feature, the most normal value obtained in each patient at any time was used in making the table.

TABLE 13
Constancy of various features in 56 nephritics (at best)

	<i>per cent</i>
Night specific gravity 1017 or less in.....	20
Variation of specific gravity 8 or less in.....	16
Maximum specific gravity 1017 or less in.....	5
Night volume 401 cc. or more in.....	5
Night volume 751 cc. or more in.....	0

These two tables together show (1) the greater constancy of the abnormal features when repeated tests are done, (2) that the maximal gravity and the night volume seem to be the *least* con-

stant abnormalities in nephritics, i.e., precisely the contrary of Mosenthal's conclusion for normals. Practically the same relative reliability of 2-hour signs is found in table 14, analogous to the last table, but taking for each feature the least normal value obtained in each patient at any time.

TABLE 14
Constancy of various features in 56 nephritics (at worst)

	<i>per cent</i>
Night specific gravity 1017 or less in.....	68
Variation of specific gravity 8 or less in.....	54
Night volume 401 cc. or more in.....	50
Maximum specific gravity 1017 or less in.....	27
Night volume 751 cc. or more in.....	25

Specific gravity when persistently low is "one of the most constant and important features" of chronic nephritis (54), and also one of the earliest as previously noted. Lowering of the highest gravity attainable was striking in nos. 3, 5, 8, 37, 46, with fixation as well in the last 4 of these.

High gravity on the other hand by no means excludes "early chronic diffuse nephritis" as shown in a recent report on a "case . . . illustrative of findings often encountered when studying nephritis" (4). The facts there given, in the protocol and charts I, II, and III, may be summarized.

Medical no. 28267, male, age thirty-four, complaint headache, Wassermann negative, fundi negative, phenolsulphonphthalein 97 per cent, albumin 1 gram per liter, casts present, no blood, blood pressure 135-90, 2-hour test on three occasions.

24-HOUR AMOUNT	NIGHT AMOUNT	NIGHT SPECIFIC GRAVITY	MAXIMUM SPECIFIC GRAVITY	VARIATION
683	309	1030	1035	6
1458	590	1022	1025	12
871	370	1027	1032	11

Similarly normal findings were surprisingly "often encountered" in the present series, as may be seen from table 15, which is the converse of table 13 above.

TABLE 15
Frequency of normal findings in 56 nephritics

	per cent
Night volume 750 cc. or less in.....	100
Night volume 400 cc. or less in.....	95
Maximum specific gravity 1018 or more in.....	95
Variation of specific gravity 9 or more in.....	84
Night specific gravity 1018 or more in.....	80

Advanced chronic nephritis with high gravity and no fixation was well shown by nos. 14 and 26. High gravity was particularly notable in four of the five cases associated with trench foot, together with decreased variations between the specimens; significance unknown; compare the averages for each column in table 16 with that for the entire series. Similar high gravity with some fixation was seen in other nephritics without trench foot (nos. 37, 48).

TABLE 16
Two-hour results in trench foot

CASE	NIGHT SPECIFIC GRAVITY (HIGHEST NOTED IN ANY TEST)	MAXIMUM SPECIFIC GRAVITY (HIGHEST NOTED IN ANY TEST)	VARIATION OF SPECIFIC GRAVITY
No. 22.....	1026	1032	6 (average of 4 tests, with average amount 1300 cc.)
No. 24.....	1028	1033	8 (980 cc.)
No. 25.....	1029	1034	7 (875 cc.)
No. 27.....	1027	1027	7 (1270 cc.)
No. 28.....	1020	1027	15 (775 cc.)
Average.....	1026	1031	9
Average, 56 cases.....	1023	1028	14

The night specific gravity shows the following order of changes:

1. Normal; as in Mason's case just cited, and in the vast majority of this series of tests.

2. Low only sometimes, and with no change in night volume nor lowered maximum gravity nor fixation: as in nos. 32, 38, 41.

3. Low generally, but as in paragraph 2 without other changes; e.g., no. 36.

4. Low sometimes with increased night volume, but no other changes; e.g., nos. 2, 3, 10, 12, 16, 18, 20, 25, 26, 28, 31.

5. Low generally, with increased night volume, but no other changes; e.g., no. 17.

6. Low generally, with maximum gravity also low generally and with fixation; e.g., nos. 5, 8, 46, 55.

Increased night volume, i.e., nocturnal polyuria (not nycturia, nocturnal pollakiuria, night frequency), has variously been interpreted as an amount exceeding 400 cc. or 750 cc. In this series the 56 highest night volumes averaged 557 cc. per patient, although 400 cc. was exceeded in only 50 per cent of the cases. It was the only abnormal feature of the two-hour test in two cases, nos. 13 and 15. When studying the night volume in several 2-hour tests on the same patient, the maximal amount (worst) is thought to be more significant than the minimal (best); since even severe cases, which in most tests give a large night volume, say, a liter, are occasionally capable of concentration. Out of the 28 patients whose worst night volume exceeded 400 cc., only 4, i.e. 14 per cent were abnormal by the best night volume. Even taking the more conservative threshold of normal we find that out of the 17 patients whose worst night volume exceeded 750 cc., only 4, i.e. 24 per cent were found nephritic according to the best night volume.

Increased twenty-four volume, i.e., total polyuria, was an inconstant sign, as the largest amount shown by each patient at any time averaged 1912 cc. and exceeded 2000 cc. in only 39 per cent of the series.

Diminished 24-hour amount, total oliguria, was similarly irregular; as the smallest recorded for each patient at any time averaged 834 cc., and was less than 1000 cc. in 71 per cent, or less than 800 cc. in 46 per cent of the cases. If we consider the earliest 24-hour amount recorded for each patient, the corresponding figures are 1330 cc. 20 per cent, and 11 per cent. If now we separate these admission 24-hour volumes into two groups: with edema and without, we find rather surprising evidence contrary to the view (59) that "the quantity . . . is notably decreased in all cases where dropsy is present," but

in agreement with Keith's (38) two resolving cases with a "moderate polyuria during the entire edematous period." In my group with edema, the 24-hour volume was:

Less than cc.	3140	3000	2500	2000	1500	1000	900	800	700	600	500	400	Total
No. patients.	3	3	4	6	11	3	1	1	0	0	0	2	34

Thus a decrease of volume was not only the exception, but was less frequent than among the 22 remaining cases without edema. For we find an average of 1450 cc, amount less than a liter in 18 per cent, or less than 800 cc in 9 per cent of those with edema; vs. in those without edema the greater tendency to oliguria so far as can be judged by the respective figures 1160 cc, 23 per cent, and 14 per cent.

Phenolsulphonphthalein test. Opsiuria (1, 60), or delayed elimination of a dye, is currently measured with methylene blue in France and phenolsulphonphthalein in the United States. Readings below 50 per cent have been widely reputed as both significant of severe involvement (usually chronic but sometimes acute) and also as constant. Low readings while significant do not however seem constant. That is, patients with other signs sufficient to predict a sub-normal output often show a value of 50 per cent or more; hence such a value should not so frequently be interpreted as excluding serious nephritis. The theory of normal tests in spite of renal disease has been thus stated: "Lewis (61) clearly showed the period of hyperactivity through which such kidneys passed before progressing into a degenerating nephritis. . . . Such findings have been rather common with us, and I think emphasize the importance of a thorough functional examination, especially for kidneys in the early stages of disease" (3). The facts have been common with others too: in one group of 100 nephritics (all with hypertension by the way) 50 per cent of those with normal phenolsulphonphthalein had albumin with or without casts and blood (62). In another group 100 per cent (3), and in the present group 96 per cent. Similarly, in the three groups, the normal phenolsulphonphthaleins showed lowered maximum gravity in 18 per cent, 33 per cent, and 4 per cent. Similarly again, in Stengel's and in this group, the normal

phenolsulphonphthalein showed systolic hypertension (150 mm. or over) in 50 per cent and 34 per cent respectively. Conversely, in the three groups, the systolic hypertensives showed normal phenolsulphonphthalein in 41 per cent, 15 per cent, and 94 per cent respectively. The normal phenolsulphonphthalein in Stengel's and in this group showed diastolic hypertension (90 mm. or over) in 100 per cent and 48 per cent. Conversely again, in the three groups, the diastolic hypertensives had normal phenolsulphonphthaleins in 40 per cent, 25 per cent, and 92 per cent respectively.

Eye-ground changes. Abnormal fundi have been reported in as much as 33 per cent of renal disease (42); also more recently in 22 per cent of nephritides (i.e., 107 cases divided as follows: retinal edema in 56, retinal exudate in 23, choroiditis in 11, retinal hemorrhages in 10, exudate around papilla in 3, old disease of optic nerve in 3, choked disc in 1) (63); or in 10 per cent of another group (64), or in 8 per cent of a third (65). In this series an ophthalmoscopic examination was made in all but 3 cases, and by the eye surgeon. He reported very slight edema of the disc in 3 patients (nos. 37, 40, 47), congenital abnormalities of the retina in 2 (nos. 36 and 56), and an old injury in 1 (no. 15). No. 47 oddly enough had no hypertension and for other reasons was thought acute nephritis. Nos. 37 and 40 had chronic disease with hypertension. Renal retinitis was then present in 5 per cent of the whole series, or in 12 per cent of the chronic cases. These percentages are less than were expected, judging by the following statement:

Fully 25 per cent of the patients with chronic Bright's disease, as examined in general hospitals, have been affected by various forms of retinitis, but if these statistics should include not only the cases of so-called typical retinitis, but also those of comparatively insignificant lesions, consisting chiefly of alterations in the walls of the retinal vessels and blurring of the disk, this percentage would be considerably higher (42).

Chloride balance. Salt retention (66) could unfortunately not be studied.

Weight. This subject is interesting from the above standpoint, and from that of the following statement on the pathogenesis of fluid accumulation:

Edema is the index of advanced hydration. . . . Between the normal hydration of a nephritic without edema and the degree of pathological hydration shown by edema, there is room for a progressive but not apparent collection of water . . . what we have called pre-edema . . . a deep infiltration oscillating from 1 to 6 kgm. (67).

In this series, edema sufficiently brawny to pit on pressure was present only in patient no. 8, but he was too sick to cross

TABLE 17

Weight

	NEPHRITICS	NORMALS
Number of cases weighed.....	55	229
Age in years.....	20-36	18-34
Weight, compared with theoretical normal:		
Low (per cent).....	16	72
High (per cent).....	82	25
Normal (per cent).....	2	3
Lowest (per cent).....	-17	-31
Highest (per cent).....	+27	+21
Average difference without regard to sign (per cent)....	10	8
Compared with enlistment weight:		
Lowest (per cent).....	-15	-18
Highest (per cent).....	+42	+25
Average difference (per cent).....	8	8

the street to be weighed. Among the remaining 55 men, the weight compared with the average normal (according to Bornhardt's formula (67)) was high in 45, i.e., 82 per cent; low in 9, i.e., 16 per cent; and exactly normal in one case. The extent of the variation from the normal is given in table 17, together with the parallel values for a series of 229 normal soldiers (68). The most remarkable difference is no. 25's gain of 42 per cent over enlistment weight. In general however the differences are not thought enough to indicate pre-edema in these patients, especially as the average gain over enlistment weight was so

nearly the same in the series of nephritics and in that of normals, i.e., about 8 per cent. Unfortunately the patients were not weighed at the time of discharge.

DIAGNOSIS

Earlier recognition. The main interest in making the observations here analyzed was the hope of recognizing obscure low-grade nephritides, especially by insistence on the value of nycturia and edema. "No sharp line could be established between what were obviously . . . nephritics, and . . . cases which one might have been tempted to describe as 'functional' or 'postural' albuminuria. All seemed to be indications of an affection of the kidneys differing in degree only" (29). This view is not only concurred in, but thought if anything too conservative. Even at the risk of the charge that a student sees his subject in everybody, attention is invited to this dictum: "It is perhaps not sufficiently recognized that renal disease may be present with few or no clinical symptoms, though evidence can often be obtained by careful laboratory investigation. On the other hand, it is now acknowledged that an acute attack may in a short time result in certain cardiac and other changes strongly suggestive of chronic disease" (69). Of the present series not one knew he had nephritis.

Type of nephritis. Differentiation in these patients has been difficult and doubtful, partly because there were no blood nitrogen, blood salt, urine salt, or postmortem studies, but more because of the current competing terms and variant meanings assigned to them (70). Some of these neologisms are: Albuminuria, cryptogenic, cyclic, digestive, fatigue, functional, hepatic, intermittent, lordotic, menstrual, orthostatic, postural, physiological, pregnancy, shower-bath, simple. Bright's disease. Kidney, amyloid, atrophic, cirrhotic, contracted, granular, indurative, leaky, red, white. Nephria. Nephritis, arterio-sclerotic, azotemic, capsular, catarrhal, degenerative, desquamative, diffuse, glomerular, hemorrhagic, hydropic, inflammatory, interstitial, intra-capillary, mixed, parenchymatous, proliferative, tubal, tubular, trench,

uremic, vascular, war. Nephropathy, hypochloruric, hypazoturic. Nephrosis, amyloid, epithelial, genuine. Renal debility, inadequacy, insufficiency, taint. Sclerosis, benign, malignant.

"It is perfectly recognized that . . . all forms of nephritis are diffuse in that every element of the tissue is somewhat affected. . . . Except in a few forms, we are ignorant of the causes of the different types of diffuse renal disease, so that it becomes difficult to classify them satisfactorily" (71). This view has been adhered to in this paper, in which all forms have been called nephritis.

COURSE

Patients with hematuria were kept in bed until a few days before evacuation, i.e., as long as two months. Improvement in these soldiers was however marked, both subjectively and objectively. Of the seventeen chronic nephritics 59 per cent felt "fine." No cases were fatal. Kidney resistance tests, of graduated work from lightest housework up to felling trees (72, 27), were not practiced. In this series the interest has been less in the immediate prognosis than in recording data, especially on the doubtful incipient cases, with a view to following-up the after-history at intervals, e.g., annually as is the practice in Professor Christian's clinic at the Peter Bent Brigham Hospital. Routine record has therefore been made of not only the patient's home address, but also the addresses of the family physician and of some friend or relative.

SUMMARY

1. The frequency of nephritis was 6 per cent of medical casualties.

2. A case-record form to facilitate systematic study is suggested.

3. The etiology seems to be: Exposure to cold and wet in 57 per cent of the patients (attention is invited to a remarkable case in which the exposure lasted only a few hours), acute infectious diseases (bronchitis, common colds, diphtheria, influenza and pneumonia) in 27 per cent, trench foot in 9 per cent, and focal

infections (chronic arthritis, otitis media and chronic tonsillitis) in 7 per cent. Less definite factors were excessive use of salt in 48 per cent, and the presence of syphilis in 7 per cent of the cases. Incidentally, of the four luetics, three were shown to have neuro-syphilis.

4. A symptom sequence is emphasized: (1) nycturia, (2) edema of the lids, (3) dyspnea, (4) edema of the feet, (5) lumbar ache, and (6) headache.

5. The constancy of two subjective symptoms was notable: nycturia and lid edema. One or both were present in 91 per cent of the patients. No other symptoms compared with these in reliability. Both were astonishingly often overlooked by patients.

6. The relative constancy of the objective signs was: albumin in 86 per cent, casts in 64 per cent, microscopic red cells in 50 per cent, hypertension in 41 per cent, low night gravity in 20 per cent, phenolsulphonphthalein in the remarkably small figure of 5 per cent. Evidence is given of the danger of excluding nephritis on the basis of absence of these abnormalities in a single test; the two-hour test also should be done at least twice. This test seemed far more trustworthy than the better known phenol-sulphonphthalein. The most valuable features of the two-hour test (done 255 times on the 56 patients) appeared to be a night gravity diminished to 1.017 or less, and a variation fixed to 8 or less. Note is made of the frequency of goiters (in the sense of thyroid enlargement) even in men accepted for the army; and attention is directed to the work of others showing the large proportion of goiters in men in general which are toxic, and to the relation of such toxic goiters to renal disease. Note is also made of the frequency of hematuria and of hypertension even in cases with excellent function, and of the infrequency of low phenolsulphonphthaleins even in cases that seemed advanced.

7. Plea is made for *earlier diagnosis* of low-grade nephritides, even when there are few or no clinical symptoms. Of these 56 cases not one had been recognized, yet 30 per cent of them seemed chronic, and of this chronic group 59 per cent "felt fine" and protested against being treated.

TABLE 18
Clinical notes
 (Cases in order of discussion under two-hour test)

CASE	DATE	SPECIMEN	24-HOUR AMOUNT	NIGHT AMOUNT	NIGHT SPECIFIC GRAVITY	24-HOUR RANGE OF VARIATION	ALBUMIN	CASTS	RED BLOOD CELLS	WHITE BLOOD CELLS	BLOOD PRESSURE	
											Systolic	Diastolic
32 Ko	December 17, 1918	Rising					vst	0	0	0	140	70
	December 19-20	2-hr.	645	425	1016	1016-31	0					
	December 21-22	2-hr.	1655	450	1017	1009-17	0					
	December 24-25	2-hr.	1870	200	1018	1009-18	0				140	70
	December 25-26	2-hr.	1420	385	1019	1010-24	0					
	December 28	Rising			1014	0		Hy. + Gr. + Hy. +	0	0		
	January 6, 1919	Rising			1029	0			0	0		
	January 16-17	2-hr.	1145	275	1013	1012-29	0				150	80
	January 17-18	2-hr.	1280	325	1015	1011-24	0					
	December 26, 1918	Rising						Hy. + Gr. +	0	+		
38 Eg	December 26-27	2-hr.	595	275	1027	1020-27	ht-t					
	December 27-28	2-hr.	510	285	1012	1012-21	t					
	December 28-29	2-hr.	1500	350	1011	1005-20	ht-spt					
	December 29-30	2-hr.	875	335	1013	1007-23	ht-vst					
	December 30-31	2-hr.	870	230	1019	1016-28	ht-vst					
	December 31-1	2-hr.	600	280	1020	1020-25	ht					
	January 1-2	2-hr.	510	265	1021	1021-30	ht					
	January 2	Rising			1020	ht		Hy. +	0	0		
	January 2-3	2-hr.	650	350	1020	1013-20	ht-t					
	January 3-4	2-hr.	1560	175	1011	1011-18	ht-spt					

TABLE 18—Continued

CASE	DATE	SPECIMEN	24-HOUR AMOUNT	NIGHT AMOUNT	NIGHT SPECIFIC GRAVITY	24-HOUR RANGE OF VARIATION	ALBUMIN	CASTS	RED BLOOD CELLS	WHITE BLOOD CELLS	BLOOD PRESSURE	
											Systolic	Diastolic
10 Le	December 9-10	2-hr.	960	575	1011	1011-24	vst					
	December 10-11	2-hr.	800	500	1014	1014-26	vst				130	65
	December 12-13	2-hr.	1085	440	1018	1017-25	vst					
	December 13-14	2-hr.	670	225	1021	1010-21	st	0	0	0		
	December 14	Rising										
	December 14-15	2-hr.	1325	450	1016	1011-19	st	0	++	++		
	December 17	Rising						Gr. +	++	++		
	December 18	Rising										
	December 18-19	2-hr.	1100	425	1011	1011-20	st	0	++	0	165	105
	December 27	Rising			1012		t	Gr. +	++	0		
	January 2, 1919	Rising			1011		t	0	++	0		
	January 11	Rising						0	++	+	155	90
	January 17-18	2-hr.	600	390	1017	1017-20	ht				150	90
	November 19, 1918	Rising						0	0	0		
	November 19-20	2-hr.	2500	950	1014	1010-22	0				120	90
	November 23-24	24-hr.	1800			1011	vst	Gr. +			110	70
	December 7-8	2-hr.	1800	500	1020	1020-27	0					
	December 8-9	2-hr.	625	115	1005	1013-30	spt	Hy. +	0	+		
	December 9	Rising										
	December 9-10	2-hr.	1285	775	1011	1011-27	0					
	December 10-11	2-hr.	1320	650	1017	1017-28	0					
	December 11-12	2-hr.	1880	500	1021	1010-25	0					
	December 12-13	2-hr.	1750	540	1011	1007-21	0				125	70
	December 13-14	2-hr.	770	300	1025	1009-28	0					

[illegible]

[illegible]

TABLE 18—Continued

CASE	DATE	SPECIMEN	24-HOUR AMOUNT	NIGHT AMOUNT	NIGHT SPECIFIC GRAVITY	24-HOUR RANGE OF VARIATION	ALBUMIN	CASTS	RED BLOOD CELLS	WHITE BLOOD CELLS	BLOOD PRESSURE	
											Systolic	Diastolic
31 Co	December 14-15	2-hr.	1010	255	1023	1012-23	0					
	December 17-18	2-hr.	1320	475	1022	1014-22	0	0	0	0		
	December 18	Rising										
	December 18-19	2-hr.	1215	775	1013	1013-30	0	0	0	0	125	80
	December 25	Rising			1016			0	0	0		
	January 6, 1919	Rising			1013			0	0	0		
	January 16-17	2-hr.	1300	285	1030	1016-30	0	0	+	+		
	January 18	Rising										
	December 8, 8191	Rising					0	Gr. ++	0	+		
	December 9-10	2-hr.	1465	275	1008	1008-26	0					
	December 10-11	2-hr.	1100	460	1009	1009-19	0				110	75
	December 14-15	2-hr.	1155	525	1008	1008-22	0					
	December 15-16	2-hr.	1555	370	1008	1008-29	0					
	December 16-17	2-hr.	1820	830	1005	1005-21	0					
	December 19-20	2-hr.	4100	2600	1010	1010-14	0					
	December 26	Rising			1013		0	0	+	0	115	65
	January 3-4	2-hr.	1360	360	1006	1006-27	0					
	January 4-5	2-hr.	775	50	1033	1005-33	0					
	January 5-6	2-hr.	1220	60	1020	1011-20	0					
	January 6	Rising					0	0	0	0		
	January 6-7	2-hr.	1575	480	1011	1005-28	0	0	0	0	120	75
	January 16	Rising										
36 Kn	December 15, 1918	Noon					t	0	0	+		

17 Un	December 20-21	2-hr.	840	320	1015	1015-32	0	0	0	0	0	155	70
	December 22	Rising			1024		0	0	0	0	0	135	70
	December 22-23	2-hr.	1650	325	1011	1008-26	0	0	0	0	0	135	70
	December 25-26	2-hr.	1235	320	1008	1008-24	0	0	0	0	0	135	70
	December 26-27	2-hr.	2225	400	1010	1005-17	0	0	0	0	0	135	70
	December 28	Rising			1010		0	0	0	0	0	135	70
	January 13, 1919	Rising					0	0	0	0	0	135	70
	January 16-17	2-hr.	910	150	1013	1013-28	0	0	0	0	0	135	70
	October 18, 1918	Rising						Hy. + Gr. +	0	0	0	135	70
	October 22	Rising			1013		st	0	0	0	0	135	70
5 Ho	October 24-25	2-hr.	1180	700	1015	1015-32	t	0	0	0	0	130	80
	October 26	24-hr.	1900			1014	0	0	0	0	0	130	75
	December 6-7	2-hr.	1405	750	1013	1013-30	0	0	0	0	0	130	70
	December 9	Rising						0	0	0	0	130	70
	November 11, 1918	Rising			1012		ht	Gr. + Gr. + Hy. +	+	+	+	145	90
	November 14	Rising			1010	1010-14	ht	+	+	+	+	145	90
	November 15-16	2-hr.	2825	850		1010-13	ht	+	+	+	+	145	90
	November 19-24	24-hrs.	4230- 2800					0	0	0	0	145	90
	November 24	Rising			1010	1011	t	0	0	0	0	145	90
	November 28-29	24-hr.	3650				ht	Gr. 4+ Gr. 4+	+	+	+	145	90
17 Un	December 1	Rising						0	0	0	0	145	90
	December 9	Rising						0	0	0	0	145	90
	December 9-10	2-hr.	1070	300	1011	1011-16	ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 10-11	2-hr.	1580	550	1012	1010-16	ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 16-17	2-hr.	1660	375	1012	1012-17	ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 20	Rising			1012		t	Gr. + Hy. + Gr. 4+	+	+	+	145	90
	December 26	Rising			1012		ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 26	Rising			1012		ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 26	Rising			1012		ht	Gr. 4+ Gr. 4+	+	+	+	145	90
	December 26	Rising			1012		ht	Gr. 4+ Gr. 4+	+	+	+	145	90

TABLE 18—Concluded

CASE	DATE	SPECIMEN	24-HOUR AMOUNT	NIGHT AMOUNT	NIGHT SPECIFIC GRAVITY	24-HOUR RANGE OF VARIATION	ALBUMIN	CASTS	RED BLOOD CELLS	WHITE BLOOD CELLS	BLOOD PRESSURE	
											Systolic	Diastolic
55 Sc	January 20, 1919	Rising			1010		ht	0	++	0		
	January 20-21	2-hr.	1285	0	0	1008-12	vst					
	January 22	Rising						0	++	0	180	100
	January 23-24	2-hr.	1055	450	1010	1006-12	spt				150	90
	January 25-26	2-hr.	1145	Lost	0	1009-12	spt					
	January 26-27	2-hr.	905	325	1010	1010-12	0					
8 Re	January 29	Rising			1012		st	Gr. ++	0	0		
	November 18, 1918	Rising			1016		st	0	++	0		
	November 18-19	2-hr.	2750	620	1014	1010-15	vst				160	95
	November 19-20	24-hr.	1900			1014	st					
	November 20-21	24-hr.	2500			1014	st					
	November 21-22	24-hr.	3200			1014	st		Smoky			
	November 22-23	24-hr.	2330			1012	t		Smoky			
	November 23-24	24-hr.	2360			1014	ht		Smoky			
	November 24-25	24-hr.	1290			1013	ht		Smoky			
	November 25-26	24-hr.	1255			1012	t				135	85
	November 26	Rising						0	+	0		
	November 26-27	24-hr.	1230			1013	t					
	November 27-28	24-hr.	750			1014	0					
	November 28-29	24-hr.	1110			1013	t					
	November 29-30	24-hr.	2280			1013	0					
	November 30-1	24-hr.	1875			1013	0					
	December 1-2	24-hr.	1250			1014	0					
	December 2-3	24-hr.	1500			1014	st					

46 Pr	December 3	Rising	2525					0	Gr. +	0	+	105	65
	December 5-6	24-hr.	1650				1012	0			+		
	December 6-7	24-hr.					1015	0			++		
	December 8	Rising						st	Gr. 4+	+			
	December 9-10	2-hr.	1735	750	1011	1011-15	1011-15	spt					
	December 10-11	2-hr.	800	180	1010	1010-12	1010-12	vst			0	115	70
	December 15	Rising							Gr. +	++			
	December 16-17	2-hr.	1995	850	1013	1011-13	1011-13	st					
	December 19-20	2-hr.	2295	720	1010	1010-13	1010-13	vst					
	December 20-21	2-hr.	2500	1150	1011	1011-13	1011-13	st				125	50
	December 27	Rising					1012	t	Hy. +	++	0		
	January 16-17	2-hr.	1430	450	1012	1012-18	1012-18	0	Gr. ++	0	+	135	85
	January 17	Rising											
	December 20-21	2-hr.	1100	170	1012	1011-13	1011-13	vst					
	December 22	Rising					1011	t	0	0	+		
	December 22-23	2-hr.	1220	0	0	1011-13	1011-13	vst					
	December 24-25	2-hr.	1380	335	1011	1011-12	1011-12	spt					
	December 25-26	2-hr.	1750	400	1013	1012-15	1012-15	st					
	December 26-27	2-hr.	1320	350	1010	1010-13	1010-13	vst					
	January 1, 1919	Rising							0	++	+	120	85
	January 11	Rising							0	++	+	140	80
	January 16-17	2-hr.	1065	200	1014	1010-16	1010-16	st				135	90
	January 22-23	2-hr.	1715	110	1012	1008-13	1008-13	vst					
	January 23-24	2-hr.	1285	0	0	1010-12	1010-12	st					
	January 24-25	2-hr.	1375	335	1011	1011-12	1011-12	spt				135	80
	January 25-26	2-hr.	1750	400	1013	1012-15	1012-15	vst					
	January 26	Rising							Gr. +	0	0		
	January 26-27	2-hr.	1320	350	1010	1010-13	1010-13	spt					

TABLE 19
Summary of clinical note tables

NUMBER AND NAME	SYMPTOMS							URINE						BLOOD PRESSURE				WEIGHT							
	Sequence							Frequency			Albumin	Casts	Red blood cells	24-hour amount		Night amount maximum in any test	Night specific gravity maximum		Maximum specific gravity	Range 2-hour specific gravity maximum	Phtalein	Systolic		Diastolic	
	Nycturia	Edematous lids	Edematous feet	Dyspnea	Lumbar ache	Headache	Night	Day	Total	Maximum				Minimum											
1 Ba	1	0	0	0	0	0	5	15	20	st	+	0	0	2090	545	875	1025	1031	15	50	135	125	75	60	- 7
2 Bk	1	0	2	0	0	0	4	8	12	ht	+	0	0	3400	1200	1000	1028	1028	17	75	145	145	85	85	+15
3 Gr	1	1	1	1	0	0	3	6	9	ht	+	+	+	4800	670	1400	1021	1029	13	50	190	120	105	65	-11
4 Zu	1	0	0	0	0	0	12	15	27	t	+	+	+	2400	870	1100	1026	1030	18	70	140	115	95	70	- 2
5 Ho	1	5	4	3	2	0	3	3	6	ht	+	+	+	4200	670	850	1012	1016	6	20	150	130	100	75	+11
6 Cl	2	0	0	0	1	0	2	5	7	t	+	0	0	1900	1300	350	1026	1027	15	75	130	120	80	65	+ 8
7 Tr	2	1	3	0	0	0	2	4	6	t	+	+	+	2100	560	330	1021	1028	15	75	140	115	85	70	+ 8
8 Re	3	2	1	2	0	4	6	5	11	ht	+	+	4+	2700	750	750	1014	1016	13	50	160	105	95	50	
9 Ck	0	2	0	0	0	1	0	4	4	t	+	+	+	2100	1500	260	1025	1030	19		125	115	80	80	+ 6
10 Le	2	4	0	3	0	1	2	8	10	vst	+	+	+	2500	585	950	1020	1030	19	70	150	110	90	70	-17
11 Wh	1	4	3	2	4	0	5	6	11	t	+	+	+	3100	800	900	1032	1032	14	70	130	115	80	60	- 3
12 Ol	2	5	5	1	3	4	2	4	6	ht	+	+	+	3100	1700	1600	1017	1029	16	80	180	140	125	65	+18
13 Ha	1	2	0	0	1	0	5	5	10	t	+	0	0	1500	1130	500	1026	1030	21	80	125	115	80	65	+ 4
14 Sp	0	0	0	0	0	0	0	5	5	t	0	+	+	1800	890	660	1025	1034	10	60	115	90	75	55	+11
15 Si	2	4	0	3	1	0	4	10	14	t	+	+	0	1800	400	750	1020	1029	17	60	130	115	75	70	- 4
16 Da	1	0	0	3	0	2	3	8	11	vst	+	+	+	2000	1300	575	1022	1025	12	75	160	145	95	70	+10
17 Un	1	2	0	0	0	3	3	2	5	t	+	0	0	1900	1200	750	1015	1035	17	65	130	125	80	70	+ 3
18 Pe	2	1	0	3	0	0	4	6	10	vst	0	0	0	2600	400	1140	1019	1030	13	60	150	115	85	65	+15
19 Do	1	0	0	3	0	2	3	5	8	st	+	+	+	2700	670	515	1019	1029	16	60	140	125	85	80	+11
20 Cf	0	3	0	1	0	2	0	4	4	ht	+	+	+	2000	710	525	1015	1026	8	60	140	120	90	70	+17
21 St	2	0	0	1	0	0	5	5	10	0	0	+	+	2200	900	845	1022	1031	16	70	130	115	65	50	+12

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